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PTOMAINES AND LEUCOMAINES,

OR THE

PUTREFACTIVE AND PHYSIOLOGICAL ALKALOIDS.

BY

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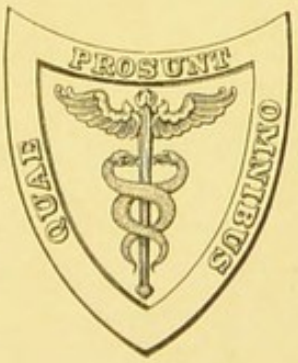

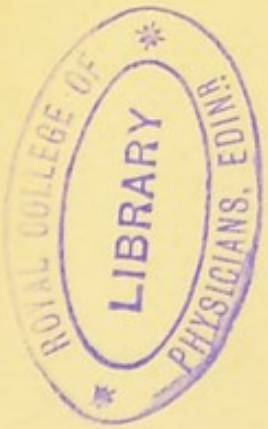

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TO

ALBERT B. PRESCOTT, PH.D., M.D., F.C.S.,

DIRECTOR OF THE CHEMICAL LABORATORY IN THE UNIVERSITY OF MICHIGAN,

THIS LITTLE WORK

IS RESPECTFULLY DEDICATED

AS A SLIGHT TOKEN OF THE HIGH ESTEEM IN WHICH

HE IS HELD BY HIS FORMER STUDENTS,

THE AUTHORS.

PREFACE.

WITHIN the past ten years much has been said and written concerning the basic substances formed during the putrefaction of organic matter, and those which are produced by the normal tissue changes in the living organism. Many investigators have given their whole time and attention to the study of these substances and important discoveries have been made and much light has been thrown upon what have heretofore been considered problems in medical science. To collect, arrange, and systematize the facts concerning ptomaines and leucomaines has been our first object. Although many short essays, some of them of great value, have been written with the above-mentioned object in view, the present work may be regarded as the first attempt to make this collation embrace everything of importance on this subject. In endeavoring to accomplish this object we have met with many difficulties. The original reports of the various investigators are scattered through the pages of medical and scientific journals, transactions of societies, monographs, government reports, etc. However, with few exceptions we have been able to obtain the original reports, and we think that we have included everything of importance published up to the present year (1888).

To the physician the facts which have been made known concerning the putrefactive and physiological alkaloids must be of great value, and if this little work furnishes the means by which members of the profession may become better acquainted with the nature of those poisons which are introduced from without, and those which are generated within the body of man, the object of its authors will be accomplished.

UNIVERSITY OF MICHIGAN, July, 1888.

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PTOMAINES AND LEUCOMAINES.

INTRODUCTION.

We may divide diseases into two classes, the infectious and the autogenous, those introduced from without and those originating within the organism. The study of the infectious diseases has been pursued with great diligence in recent years, and many brilliant results have been reached, but the question, How do germs induce disease? remained without a satisfactory answer until it was discovered that they produce, by their growth, chemical poisons, ptomaines, that the absorption of these poisons is followed by the symptoms of the disease, and that each specific, pathogenic microörganism produces its own characteristic poison. In infectious diseases the chemical poison is really formed within the body, but the active agent, the germ, causing the formation of the poison, is introduced from without. It is, therefore, proper to speak of these diseases as having their origin outside of the body. Their spread is to be arrested by the destruction of the germ, by isolation and disinfection. Their treatment consists of attempts to destroy the microörganism which has already found lodgement within the body, or, failing in this, to antagonize the effects of the poison and to maintain life until the germ, weakened by successive generations of growth or poisoned

by its own products, ceases to manifest its ill effects, and the disease terminates by self-limitation.

On the other hand, the autogenous diseases owe their existence to disturbances between tissue metabolism and excretion. They are prevented by keeping these functions of the body in harmony. They are treated by hastening elimination or by retarding or modifying metabolism or by both.

CHAPTER I.

DEFINITION AND HISTORICAL SKETCH OF THE PTOMAINES.

DEFINITION.— A ptomaine is a chemical compound which is basic in its character, and which is formed during the putrefaction of organic matter. The name was suggested by SELMI, and is derived from the Greek word πτῶμα (cadaver). On account of their basic properties, in which they resemble the vegetable alkaloids, ptomaines may be called putrefactive alkaloids. They have been called animal alkaloids, but this is a misnomer, because some ptomaines are formed by the putrefaction of vegetable matter, as will be shown further on. While some of the ptomaines are highly poisonous, this is not an essential property, for others are wholly inert. Indeed, the greater number of those which have been isolated up to the present time are not poisonous. On the other hand, all poisonous substances formed during putrefaction are not ptomaines. Thus phenol and hydrogen sulphide are poisonous products of putrefaction, but are not ptomaines.

All ptomaines contain nitrogen as an essential part of their basic character. In this, also, they resemble the vegetable alkaloids. Some of them contain oxygen, while others do not. The latter correspond to the volatile vegetable alkaloids, nicotine, and coniine, and the former correspond to the fixed alkaloids.

Since all putrefaction is due to the action of bacteria, it follows that all ptomaines result from the growth of these microörganisms. The kind of ptomaine formed will de-

pend upon the individual bacterium engaged in its production, the nature of the material being acted upon by the bacterium, and the conditions under which the putrefaction goes on, such as the temperature, amount of oxygen present, the electrical conditions existing, and the duration of the process. Only the bacillus of typhoid fever (EBERTH'S bacillus), so far as is known at least, can produce the ptomaine typhotoxine, and the special bacterium of tetanus seems to be necessary in order to produce tetanine, a ptomaine which, when injected under the skin of the animal, causes tetanic convulsions. BRIEGER found that, although the typhoid bacillus grew well in solutions of peptone, it did not produce any ptomaine; while from cultures of the same bacillus in beef-tea he obtained a poisonous alkaloid. FITZ found that whilst the bacillus butyricus produces by its action on carbohydrates butyric acid, in glycerine it produces propylic alcohol, and MORIN has found amyl alcohol among the products of the action of this germ. BROWN has shown that while the mycoderma aceti converts ethylic alcohol into acetic acid, it converts propylic alcohol into propionic acid, and is without effect upon methylic alcohol, primary isobutylic alcohol, and amylic alcohol. Some bacteria will not multiply below a given temperature. Thus, the bacillus butyricus will not grow at a temperature below 24°.[1] The lower temperature does not destroy the organism, but it lies dormant until the conditions are more favorable for its growth. PASTEUR divided the bacteria into two classes, the aërobic and the anaërobic. As the name implies, the former grow and thrive in the presence of air, while the latter find their conditions of life improved by the

[1] All temperatures given in this work are Centigrade unless otherwise specified.

exclusion of air. Therefore, different ptomaines will be formed in decomposing matter feeely exposed to the air, and in that which is buried beneath the soil or from which the air is largely excluded. Even when the same ferment is present, the products of the putrefaction will vary, within certain limits, according to the extent to which the putrefying material is supplied with air. The kind of ptomaine found in a given putrid substance will depend also upon the stage of the putrefaction. Ptomaines are transition products in the process of putrefaction. They are temporary forms through which matter passes while it is being transformed, by the activity of bacterial life, from the organic to the inorganic state. Complex organic substances, as muscle and brain, are broken up into less complex molecules, and so the process of chemical division goes on until the simple and well-known final products, carbonic acid gas, ammonia, and water, result; but the variety of combinations into which an individual atom of carbon may enter during this long series of changes is almost unlimited, and with each change in combination there is more or less change in nature. In one combination the atom of carbon may exist as a constituent of a highly poisonous substance, while the next combination into which it enters may be wholly inert.

It was formerly supposed that putrefaction was simply oxidation, but the researches of PASTEUR and others have demonstrated the fact that countless myriads of minute organisms are engaged constantly in transforming matter from the organic to the inorganic form. Lock up the bit of flesh so that these little workers cannot reach it, and it will remain unchanged indefinitely.

It may be asked if any of the changes occurring during putrefaction are to be regarded as purely chemical. Without

doubt, many of the secondary products of putrefaction arise from reactions between antecedent and more complex products, or by the action of oxygen, water, and reducing agents upon primary products. Ptomaines formed in this way may be regarded as the indirect results of bacterial life.

Historical Sketch.—It must have been known to primitive man that the eating of putrid flesh was liable to affect the health more or less seriously; and when he began his endeavors to preserve his food for further use, instances of poisoning from putrefaction must have multiplied. However, the distinguished physiologist Albert von Haller seems to have been the first to make any scientific experiments concerning the effects of putrid matter upon animals. He injected aqueous extracts of putrid material into the veins of animals and found that death resulted. Later in the eighteenth century, Morand gave an account of the symptoms induced by eating poisonous meat. In the early part of the present century (1808 to 1814), Gaspard carried on similar experiments. He used as material the putrid flesh of both carnivorous and herbivorous animals. With these he induced marked nervous disturbances, as stiffness of the limbs, opisthotonos, and tetanus. Gaspard concluded from the symptoms that the poisonous effects were not due to carbonic acid gas or hydrogen sulphide, but thought it possible that ammonia might have part in their production. In 1820, Kerner published his first essay on poisonous sausage, which was followed by a second in 1822. At first he thought that the poisonous properties were due to a fatty acid, similar to the sebacic of Thenard, and which originated during putrefaction. Later he modified these views, and believed the

poison to be a compound consisting of the sebacic acid and a volatile principle. This may be regarded as the first suggestion as to the probability of the development of a poisonous substance with basic properties in decomposing matter. In 1822, DUPRÉ observed a peculiar disease among the soldiers under his care, who, during the very warm and dry summer of that year, were compelled to drink very foul water. Later, MAGENDIE, induced by the investigations of GASPARD and the observations of DUPRÉ, made many experiments, in which dogs and other animals were confined over vessels containing putrid animal matter and compelled constantly to breathe the emanations therefrom. The effects varied markedly with the species of animal and the nature of the putrid material, but in some instances symptoms were induced which resembled closely those of typhoid fever in man. LEURET directed his attention to the chemical changes produced in blood by putrefaction, but accomplished nothing of special value. DUPUY injected putrid material into the jugular vein of a horse, and with TROUSSEAU studied alterations produced in the blood by these injections.

During the third decade of the present century there were many investigators in addition to those mentioned above, who endeavored to ascertain the active agent in poisonous foods. DANN, WEISS, BÜCHNER, SCHUMANN, CADET DE GASSICOURT, and ORFILA studied poisonous sausage, but made no advance upon the work done by KERNER. HENNEMAN, HÜNNEFELD, WESTRUMB, and SERTÜRNER made contributions concerning poisonous cheese, but all believed the caseic acid of KERNER to be the poisonous principle.

In 1850, SCHMIDT, of Dorpat, made some investigations on the decomposition products and volatile substances

found in cholera stools; and, two years later, MEYER, of Berlin, injected the blood and stools of cholera patients into lower animals. In 1853, STICH made an important contribution on the effects of acute poisoning with putrid material. He ascertained that, when given in sufficient quantity, putrid matter produces an intestinal catarrh, with choleraic stools. Nervous symptoms, trembling, unsteady gait, and finally convulsions, were also observed. STICH made careful post-mortem examinations, and was unable to find any characteristic or important lesion. Theoretically, he concluded that the putrid material contained a ferment which produced rapid decomposition of the blood.

In 1856, PANUM published a most important contribution to the knowledge of the nature of the poison present in putrid flesh. He first demonstrated positively the chemical character of the poison, inasmuch as he showed that the aqueous extract of the putrid material retained its poisonous properties after treatment which would insure the destruction of all organisms. His conclusions were as follows:

(1) "The putrid poison contained in the decomposed flesh of the dog, and which is obtained by extraction with distilled water and repeated filtration, is not volatile, but fixed. It does not pass over on distillation, but remains in the retort."

(2) "The putrid poison is not destroyed by boiling, nor by evaporation. It preserves its poisonous properties even after the boiling has been continued for eleven hours, and after the evaporation has been carried to complete desiccation at 100°."

(3) "The putrid poison is insoluble in absolute alcohol, but is soluble in water, and is contained in the aqueous extract which is formed by treating with distilled water

the putrid material which has previously been dried by heat and washed with alcohol."

(4) "The albuminoid substances which frequently are found in putrid fluids are not in themselves poisonous only so far as they contain the putrid poison fixed and condensed upon their surfaces, from which it can be removed by repeated and careful washing."

(5) "The intensity of the putrid poison is comparable to that of the venom of serpents, of curare, and of certain vegetable alkaloids, inasmuch as 0.012 of a gram of the poison, obtained by extracting with distilled water putrid material which had been previously boiled for a long time, dried at 100° and submitted to the action of absolute alcohol, was sufficient almost to kill a small dog."

PANUM made intravenous injections with this poison, and with ammonium carbonate, ammonium butyrate, ammonium valerianate, tyrosine, and leucine, and found that the symptoms induced by the putrid poison differed from those caused by the other agents. Moreover, he found the symptoms to differ from those of typhoid fever, cholera, pyæmia, anthrax, and sausage poisoning. He was also in doubt as to whether the poison acted directly upon the nervous system, or whether it acted as a ferment upon the blood, causing decomposition, the products of which affected the nerve-centres; but he was sure that it could not correspond to the ordinary ferments, inasmuch as it was not decomposed by prolonged boiling nor by treatment with absolute alcohol. Certainly, the putrid poison could not consist of a living organism.

The symptoms observed by PANUM varied greatly with the quantity of the poison used and the strength of the animal. After the intravenous injection of large doses, death followed in a very short time. In these cases there

were violent cramps, and involuntary evacuations of the urine and fæces; the respirations were labored, the pallor was marked, sometimes followed by cyanosis, the pulse feeble, the pupils widely dilated, and the eyes projecting. In these cases the autopsy did not reveal any lesion, save that the blood was dark, imperfectly coagulated and slightly infiltrated through the tissue. Post-mortem putrefaction came on with extraordinary rapidity.

When smaller doses or more vigorous animals were used, the symptoms did not appear before from a quarter of an hour to two hours, and sometimes even later. In these cases the symptoms were less violent, and the animal generally recovered. In all instances, however, the disturbances were more or less marked.

In addition to the "putrid poison," PANUM obtained a narcotic substance, the two being separated by the solubility of the narcotic in alcohol. The alcoholic extract was evaporated to dryness, the residue dissolved in water and injected into the jugular vein of a dog. The animal fell into a deep sleep, which remained unbroken for twenty-four hours, when it awoke apparently in perfect health.

PANUM'S first contributions, which were published in Danish, did not attract the attention which they deserved, until after the lapse of several years. Now, however, their importance is fully appreciated, and the distinguished investigator lived to receive the credit and honor due him.

WEBER in 1864, and HEMMER and SCHWENNINGER in 1866, confirmed the results obtained by PANUM; and SCHWENNINGER announced that in the various stages of putrefaction different products are formed, and that these vary in their effects upon animals. In 1866, BENCE JONES and DUPRÉ obtained from the liver a substance which in solutions of dilute sulphuric acid gives the blue

fluorescence observed in similar solutions of quinine. To this substance they gave the name "animal chinoidine." Subsequently, the same investigators found this substance in all organs and tissues of the body, but most abundantly in the nerves. Its feebly acid solutions give precipitates with iodine, potassio-mercuric iodide, phosphomolybdic acid, gold chloride, and platinum chloride. From three pounds of sheep's liver, they obtained three grams of a solution in which, after slight acidulation with sulphuric acid, the intensity of the fluorescence was about the same as that of a similarly acidulated solution of quinine sulphate which contained 0.2 gram of quinine per litre. Still later, this base was obtained by MARINO-ZUCO.

In 1868, BERGMANN and SCHMIEDEBERG separated, first from putrid yeast, and subsequently from decomposed blood, in the form of a sulphate, a poisonous substance which they named sepsine. The sulphate of sepsine forms in needle-shaped crystals. Small doses (0.01 gram) of this substance were dissolved in water and injected into the veins of two dogs. In a short time it produced vomiting, and later diarrhœa, which, in one of the animals, after a time, became bloody. Post-mortem examination showed, in the stomach and intestines, bloody ecchymoses. It was now believed that the "putrid poison" of PANUM had been isolated, and that it was identical with sepsine, but further investigations showed that this was not true. There are marked differences in their effects upon animals, and sepsine has not been found to be generally present in putrid material. It is only rarely found in blood, and the closest search has failed to show its presence in pus. BERGMANN, following the same method which he had used in extracting this poison from yeast, has been unable to obtain it from other putrid material. Moreover, he was not

always successful in obtaining the poison from yeast. Sepsine was not obtained in quantity sufficient to serve for an ultimate analysis, hence, its composition remains unknown.

In 1869 ZÜLZER and SONNENSCHEIN prepared from decomposed meat extracts a nitrogenous base, which in its chemical reactions and physiological effects resembled atropine and hyoscyamine. When injected under the skin of animals it produced dilatation of the pupils, paralysis of the muscles of the intestines, and acceleration of the heart-beat; but it is uncertain and inconstant in its action. This probably results from rapid decomposition taking place in it, or to variations in its composition at different stages of putrefaction. This substance has also been obtained from the bodies of those who have died from typhoid fever, and it may be possible that the belladonna-like delirium which frequently characterizes the later stages of this disease is due to the ante-mortem generation of this poison within the body.

Since 1870 many chemists have been engaged in making investigations on the products of putrefaction. We can only mention a few names at present, while others will be referred to subsequently in discussing the individual ptomaines.

First of all stands the Italian SELMI, who suggested the name ptomaine, and whose researches furnished us with much information of value, and, what is probably of more importance, gave an impetus to the study of the chemistry of putrefaction, which has already been productive of much good and gives promise of much more in the future. SELMI showed that ptomaines could be obtained (1) by extracting acidified solutions of putrid material with ether; (2) by extracting alkaline solutions with ether; (3) by extracting alkaline solutions with chloroform; (4) by extracting with

amylic alcohol; and (5) that there yet remained in the solutions of putrid matter ptomaines which were not extracted by any of the above-mentioned reagents. In this way he gave some idea of the great number of alkaloidal bodies which might be formed among the products of putrefaction, and the promising field thus discovered and outlined was soon occupied by a busy host of chemists. In the second place, he demonstrated the fact that many of the ptomaines give reactions similar to those given by the vegetable alkaloids. This led the toxicologist into investigations, the results of some of which we will ascertain further on.

SELMI, however, did not succeed in isolating completely a single putrefactive alkaloid. All his work was done with extracts. He remained ignorant, except in a general way, of the composition of these bodies. NENCKI, in 1876, made the first ultimate analysis and determined the first formula of a ptomaine. This was an isomer of collidine, which will be described later.

RÖRSCH and FASSBENDER, in a case of suspected poisoning, obtained by the STAS-OTTO method a liquid which could be extracted from acid as well as alkaline solutions by ether, and which gave all the general alkaloidal reactions. They were unable to crystallize either extract by taking it up with alcohol and evaporating. The colorless aqueous solution was not at all bitter to the taste. The precipitate formed with phosphomolybdic acid dissolved on the application of heat, giving a green solution, which became blue on the addition of ammonia. They believed that this substance was derived from the liver, since fresh ox-liver, treated in the same manner, gave them an alkaloid which could be extracted with ether from acid as well as from alkaline solutions. GUNNING found this same alkaloid in liver-sausage from which poisoning had occurred.

RÖRSCH and FASSBENDER state that while in some of its reactions this substance resembles digitaline, it is distinguished from this vegetable alkaloid by the failure of the ptomaine to give the characteristic bitter taste.

SCHWANERT, whilst examining the decomposing intestines, liver, and spleen of a child which had died suddenly, perceived a peculiar odor and obtained by the STAS-OTTO method (ether extract from an alkaline solution) small quantities of a base, which was distinguished from nicotine and coniine by its greater volatility and its peculiar odor. He supposed that this substance was produced by decomposition, and, in order to ascertain the truth of his supposition, he took the organs of a cadaver that had lain for sixteen days at a temperature of 30°, and was well decomposed. These were treated with tartaric acid and alcohol. The acid solution was first extracted with ether, and yielded no result, it was then rendered alkaline and extracted with ether. The latter extract gave, on evaporation, the same substance which he had found in the organs of the child. The residue was a yellowish oil, having an odor somewhat similar to propylamine. It was repulsive, but not bitter to the taste, and alkaline in reaction. On the addition of hydrochloric acid, it crystallized in white needles, which were freely soluble in water, but soluble with difficulty in alcohol. On the addition of ammonium hydrate to this crystalline substance, a white vapor of unpleasant odor was given off. The crystals dissolved in sulphuric acid, forming a solution which was at first colorless, but which gradually became dirty brownish-yellow, and grayish-brown on the application of heat. On being warmed with sodium molybdate, a splendid blue color, becoming gradually gray, was produced. Potassium bichromate and sulphuric acid gave a reddish-brown, then a grass-green color.

Nitric acid gave a yellow color. A tartaric acid solution of the crystals produced, on the addition of platinum chloride, a dirty yellow precipitate of small six-sided stars, which contained 31.55 per cent. of platinum. Gold chloride gave a pale yellow, amorphous precipitate; mercuric chloride yielded white crystals; potassio-mercuric iodide a dirty white precipitate; and potassio-cadmic iodide yielded no result. Tannic acid produced only a turbidity. Sodium phosphomolybdate gave a yellow, flocculent precipitate, which became blue on the addition of ammonium hydrate. This base has a slight reducing power, and in this it resembles a substance obtained by SELMI, but it differs from SELMI's extract inasmuch as it does not give a violet coloration on being warmed with sulphuric acid. In its amorphous character, its behavior to the general alkaloidal reagents, and its lack of bitter taste, it resembles the base obtained by RÖRSCH and FASSBENDER, but, unlike that alkaloid, it is extractable from alkaline solutions only.

SELMI, in eommenting upon the base studied by RÖRSCH and FASSBENDER, SCHWANERT, and himself, believing that all were dealing with the same body, states that it does not contain phosphorus, and that it is separated with extreme difficulty from the vegetable alkaloids.

LIEBERMANN, in examining the somewhat decomposed stomach and intestines in a case of suspected poisoning, found an alkaloidal body which was unlike that studied by the chemists mentioned above, inasmuch as it was not volatile. The STAS-OTTO method was employed. The ether extract from alkaline solution left, on evaporation, a brownish, resinous mass, which dissolved in water to a turbid solution, the cloudiness increasing on heating. This reaction agrees with coniine, but the odor differed from that of

the vegetable alkaloid. The aqueous, strongly alkaline solution gave the following reactions:

(1) With tannic acid, a white precipitate.

(2) With potassium iodide, a yellowish-brown, turning to dark brown precipitate.

(3) With chlorine water, a marked white cloudiness.

(4) With phosphomolybdic acid, a yellow precipitate.

(5) With potassio-mercuric iodide, a white precipitate.

(6) With mercuric chloride, a white cloudiness.

(7) With concentrated sulphuric acid, after a while, a reddish-violet coloration.

(8) With concentrated nitric acid, after evaporation, a yellowish spot.

These reactions exclude all vegetable alkaloids save coniine. The putrefactive alkaloid does not distil when heated on the oil-bath to 200°, while coniine distils at 135°. The former is with certainty distinguished from coniine by its non-poisonous properties.

This substance is extracted by ether from acid, as well as from alkaline solutions. The yellow, oily drops obtained after the evaporation of the ether are soluble in alcohol. The taste is slightly burning.

SELMI obtained from both putrefying and fresh intestines a substance which gave the general alkaloidal reactions with potassium iodide, gold chloride, platinum chloride, potassio-mercuric iodide, and phosphomolybdic acid. It has strong reducing power, and when warmed with sulphuric acid gives a violet coloration. These reactions are not due to leucine, tyrosine, creatine, or creatinine. This is the substance which, as has been stated, SELMI considered identical with that observed by RÖRSCH and FASSBENDER and SCHWANERT. The minor differences observed by the different chemists may have been due to the varying

degrees of purity in which the substance was obtained by them.

From human bodies which had been dead from one to ten months, SELMI removed many alkaline bases. From an ether solution of a number of these, one was removed by treatment with carbonic acid gas. One base which was insoluble in ether, but readily soluble in amylic alcohol, was found to be a violent poison, producing in rabbits, tetanus, marked dilatation of the pupils, paralysis, and death.

Parts of a human body preserved in alcohol were found by SELMI to yield an easily volatile, phosphorus-containing substance, which is soluble in ether and carbon disulphide, and gives a brown precipitate with silver nitrate. It is not the phosphide of hydrogen. A similar substance is produced by the slow decomposition of the yolks of eggs. With potassium hydrate it gives off ammonia and yields a substance having an intense coniine odor. It is volatile and reduces phosphomolybdic acid.

SELMI also obtained from decomposing egg-albumen a body, whose chloride forms in needles, and which has a curare-like action on frogs. From one arsenical body which had been buried for fourteen days, he obtained, by extracting from an alkaline (made alkaline with baryta) solution with ether, a substance which formed in needles and which gave crystalline salts with acids. With sulphuric acid it gave a red color; with iodic acid and sulphuric acid it liberated free iodine and gave a violet coloration; with nitric acid it gave a beautiful yellow, which deepened on the addition of caustic potash. Platinum chloride gave no precipitate save in highly concentrated solutions. From a second arsenical body, SELMI obtained by the same method a substance which gave, with tannic acid, a white precipi-

tate; with iodine in hydriodic acid a kermes-brown; with gold chloride a yellow, which was soon reduced; with mercuric chloride a white; with picric acid a yellow, which gradually formed in crystalline tablets. This substance did not contain any arsenic, but was highly poisonous. From the stomach of a hog, which had been preserved in a solution of arsenious acid, SELMI separated an arsenical organic base. The fluid was distilled in a current of hydrogen. The distillate, which was found to be strongly alkaline, was neutralized with hydrochloric acid and evaporated to dryness, when cross-shaped crystals, giving an odor similar to that of trimethylamine, were obtained. This substance was found by CIACCIA to be highly poisonous, producing strychnia-like symptoms. With iodine in hydriodic acid it is said to give a gray, crystalline precipitate.

From the liquid which remained in the retort, a non-volatile arsenical ptomaine was extracted with ether. An aqueous solution of this gave with tannic acid a slowly forming, yellowish precipitate, and similarly colored precipitates with iodine in hydriodic acid, platinum chloride, auric chloride, mercuric chloride, potassio-mercuric iodide, potassio-bismuthic iodide, picric acid, and potassium bichromate. The physiological action of this substance as demonstrated on frogs was unlike that of the arsines, but consisted of torpor and paralysis.

MORIGGIA and BATTISTINI experimented with alkaloids obtained from decomposing bodies upon guinea-pigs and frogs, but did not attempt their isolation because of the rapid decomposition which they undergo when exposed to the air and by which they lose their poisonous properties. These alkaloids they found to be easily soluble in amylic alcohol, less soluble in ether.

In 1871 LOMBROSO showed that the extract from mouldy

corn-meal produced tetanic convulsions in animals. This threw some light upon the cases of sporadic illness which had long been known to occur among the peasants of Lombardy, who eat fermented and mouldy corn-meal. In 1876 BRUGNATELLI and ZENONI obtained by the STAS-OTTO method from this mouldy meal an alkaloidal substance which was white, non-crystalline, unstable, and insoluble in water, but readily soluble in alcohol and ether. With sulphuric acid and bichromate of potassium it yields a color reaction very similar to that of strychnine.

The action of the ether extracts from decomposed brain resembles that of curare, but is less marked and more transitory. The beats of the frog's heart were decreased in number and strengthened in force; the nerves and the muscles lost their irritability, and the animal passed into a condition of complete torpor. The pupils were dilated. GUARESCHI and MOSSO, using the STAS-OTTO method, obtained from human brains which had been allowed to decompose at a temperature of from 10° to 15° for from one to two months, both volatile and non-volatile bases. Among the former only ammonia and trimethylamine were in sufficient quantity for identification. With these, however, were minute traces of ptomaines.

They obtained non-volatile bases from both acid and alkaline solutions. From the former, they separated a substance which gave precipitates with gold chloride, phosphotungstic acid, phosphomolybdic acid, MAYER'S reagent, palladium chloride, picric acid, iodine in potassium iodide, and slightly with tannic acid. This substance was not precipitated with platinum or mercury.

From the alkaline extract there was obtained a substance which in dilute hydrochloric acid solutions gave with gold chloride a heavy yellow precipitate with reduction, also

precipitates with phosphomolybdic acid, platinum chloride, MAYER'S reagent, picric acid, phosphotungstic acid, MARMÉ'S reagent, iodine in potassium iodide, tannin, bichromate of potassium, palladium chloride, and mercuric chloride. It reduces ferric salts. From decomposed fibrin the same investigators obtained one well-defined ptomaine. Analyses of the platinum compound of this substance gave the formula $C_{10}H_{15}N$. This substance will be discussed in a future chapter.

From fresh brain substance they separated ammonia, trimethylamine, and an undetermined base. These, however, are not to be regarded as products of putrefaction, but as resulting from the action of the reagents upon the brain substance. The trimethylamine probably arises from the splitting up of lecithin, while the undetermined base is most likely choline, which also results from the breaking up of the lecithin molecule.

They also show that when DRAGENDORFF'S method is used basic substances can be obtained from fresh meat, and these are shown to be produced by the action of the sulphuric acid on the flesh.

To BRIEGER, of Berlin, is due the credit of isolating and determining the composition of a number of ptomaines. From putrid flesh he obtained neuridine, $C_5H_{14}N_2$, and neurine, $C_5H_{13}NO$. The former is inert, while the latter is poisonous. From decomposed fish he separated a poisonous base, $C_2H_4(NH_2)_2$, which is an isomeride of ethylenediamine, muscarine, $C_5H_{15}NO_3$, and an inert substance, $C_7H_{17}NO_2$, gadinine. Rotten cheese yielded neuridine and trimethylamine. Decomposed glue gave neuridine, dimethylamine, and a muscarine-like base. In the cadaver, he has found in different stages of decomposition, choline, neuridine, trimethylamine, cadaverine, $C_5H_{14}N_2$, putrescine, $C_4H_{12}N_2$, and

saprine, $C_5H_{16}N_2$. These are all inert. After fourteen days of decomposition he found a poisonous substance, mydaleine. From a cadaver which had been kept at from $-9°$ to $+5°$ C. for four months, BRIEGER obtained mydine, $C_8H_{11}NO$, the poisonous substance mydatoxine, $C_6H_{13}NO_2$, also the poison methyl-guanidine. From poisonous mussel he separated mytilotoxine, $C_6H_{15}NO_2$. From pure cultures of the typhoid bacillus of KOCH and EBERTH, BRIEGER obtained a poison, typhotoxine, and, from like cultures of the tetanus germ of ROSENBACH, tetanine. All of these bases will be discussed in detail in a subsequent chapter.

GAUTIER and ETARD have also isolated ptomaines which will be described later.

In 1885, VAUGHAN succeeded in isolating the active agent of poisonous cheese, to which he gave the name tyrotoxicon. This discovery has been confirmed by NEWTON, WALLACE, SCHÆFFER, STANTON, FIRTH, LADD, and WOLFF.

NICATI and RIETSCH, KOCH, and others, have shown the presence of a poisonous substance in cultures of the cholera bacillus. SALMON and SMITH have done the same with cultures of the hog cholera germ; HOFFA, with those of the anthrax bacillus; and BRIEGER with those of the tetanus germ.

CHAPTER II.

FOODS CONTAINING POISONOUS PTOMAINES.

Poisonous Mussels.—Judging from the symptoms produced, there seem to be three different kinds of poisonous mussel. In one class, the symptoms resemble those of a true gastro-intestinal irritant. Fodere reports the case of a sailor, who, after eating a large dish of mussels, suffered from nausea, vomiting, pain in the stomach, tenesmus, and rapid pulse. After death, which occurred within two days, the stomach and intestines were found inflamed and filled with a tenacious mucus. Combe and others also report cases of the choleraic form of poisoning from mussel.

However, the symptoms which most frequently manifest themselves after the eating of poisonous mussels are more purely nervous. A sensation of heat and itching appears usually in the eyelids, and soon involves the whole face, and perhaps a large portion of the body. An eruption, usually called nettle-rash, though it may be papular or vesicular, covers the parts. The itching is most annoying, and may be accompanied by marked swelling. There follows a distressing asthmatic breathing, which is relieved by ether. In some cases reported by Mohring, dyspnœa preceded the eruption, the patients became insensible, the face livid, and convulsive movements of the extremities were noticed. Burrow reports similar cases with delirium, convulsions, coma, and death within three days.

In a third class of cases, there may be a kind of intoxi-

cation resembling somewhat that of alcohol, then paralysis, coma, and death.

In 1827, COMBE observed thirty persons poisoned, two of them fatally, with mussels. He describes the symptoms as follows: "None, so far as I know, complained of anything peculiar in the smell or taste of the animals, and none suffered immediately after taking them. In general, an hour or two elapsed, sometimes more; and the bad effects consisted rather in uneasy feelings and debility, than in any distress referable to the stomach. Some children suffered from eating only two or three; and it will be remembered that Robertson, a young and healthy man, only took five or six. In two or three hours they complained of a slight tension at the stomach. One or two had cardialgia, nausea, and vomiting; but these were not general, or lasting symptoms. They then complained of a prickly feeling in their hands, heat and constriction of the mouth and throat; difficulty of swallowing and speaking freely; numbness about the mouth, gradually extending to the arms, with great debility of the limbs. The degree of muscular debility varied a good deal, but was an invariable symptom. In some it merely prevented them from walking firmly, but in most of them it amounted to perfect inability to stand. While in bed they could move their limbs with tolerable freedom, but on being raised to the perpendicular posture they felt their limbs sink under them. Some complained of a bad, coppery taste in the mouth, but in general this was in answer to what lawyers call a leading question. There was slight pain of the abdomen, increased on pressure, particularly in the region of the bladder, which organ suffered variously in its functions. In some the secretion of urine was suspended, in others it was free, but passed with pain and great effort. The action of the heart was

feeble; the breathing unaffected; the face pale, expressive of much anxiety; the surface rather cold; the mental faculties unimpaired. Unluckily, the two fatal cases were not seen by any medical person; and we are, therefore, unable to state minutely the train of symptoms. We ascertained that the woman, in whose house were five sufferers, went away as in a gentle sleep, and that a few moments before death she had spoken and swallowed."

The woman died within three hours, and the other death was that of a watchman who was found dead in his box six or seven hours after he had eaten the mussels. Post-mortem examination in these showed no abnormality. The stomach contained some of the food partially digested.

The explorer VANCOUVER reports four cases similar to those observed by COMBE. One of the sailors died in five and a half hours after eating the mussels.

In some recent cases reported by SCHMIDTMANN, as quoted by BRIEGER, the symptoms were as follows: Some dock hands and their families ate of cooked blue mussels which had been taken near a newly built dock. The symptoms appeared, according to the amount eaten, from soon after eating to several hours later. There was a sensation of constriction in the throat, mouth, and lips; the teeth were set on edge as though sour apples had been eaten. There was dizziness, no headache; a sensation of flying, and an intoxication similar to that produced by alcohol. The pulse was hard, rapid (eighty to ninety), no elevation of temperature, the pupils dilated and reactionless. Speech was difficult, broken and jerky. The limbs felt heavy; the hands grasped spasmodically at objects and missed their aim. The legs were no longer able to support the body, and the knees knocked together. There was nausea, vomiting, no abdominal pain, no diarrhœa. The

hands became numb and the feet cold. The sensation of cold soon extended over the entire body, and in some the perspiration flowed freely. There was a feeling of suffocation, then a restful and dreamless sleep. One person died in one and three-quarters of an hour, another in three and one-half hours, and a third in five hours, after eating of the mussels.

In one of these fatal cases rigor mortis was marked and remained for twenty-four hours. The vessels of all the organs were distended, only the heart was empty. VIRCHOW concluded from the conditions observed that the blood had absorbed oxygen with great avidity. There was marked hyperæmia and swelling of the mucous membrane of the stomach and intestines, which VIRCHOW pronounced an enteritis. The spleen was enormously enlarged and the liver showed numerous hemorrhagic infarctions.

Many theories have been advanced to account for poisonous mussels. It was formerly believed that the effects were due to copper which the animals obtained from the bottoms of vessels; but, as CHRISTISON remarks, copper does not produce these symptoms. Moreover, CHRISTISON made analysis of the mussels which produced the symptoms observed by COMBE, and was unable to detect any copper. BOUCHARDAT found copper in some poisonous mussels, but he does not state the amount of the copper nor the source of the animals.

EDWARDS advanced the theory that the symptoms were wholly due to idiosyncrasy in the consumer. This may be true in some instances where only one or two of those partaking of the food are affected, but it certainly is not a tenable hypothesis in such instances as those reported by COMBE and SCHMIDTMANN, where a large number or all those who partook of the food were affected.

Coldstream found the livers of the Leith mussels, as he thought, larger, darker, and more brittle than normal, and to this diseased condition he attributed the ill effects.

Lamoroux, Mohring, de Beume, Chenu, and du Rondeau have supposed that the poisonous effects were due to a particular species of medusæ upon which the mussels feed. De Beume found in the vomited matter of one person, suffering from mussel poisoning, some medusæ, and he states that these are most abundant during the summer, when mussels are most frequently found to be poisonous.

The theory of Burrow that the animal is always poisonous during the period of reproduction has been received with considerable credit. However, cases of poisoning have occurred at different seasons of the year.

Crumpe, in 1872, suggested that there is a species of mussel which is in and of itself poisonous, and this species is often mixed with the edible variety. Schmidtmann and Virchow support this idea. They state that the poisonous species has a brighter shell, a sweeter, more penetrating, bouillon-like odor than the edible kind, also that the flesh of the former is yellow and that the water in which they are cooked is bluish. Lohmeyer also champions this opinion. This theory, however, is opposed by the majority of zoölogists. Möbius states that the peculiarities of the supposed poisonous variety pointed out by Virchow and Schmidtmann are really due to the conditions under which the animal lives, the amount of salt in the water, the temperature of the water, whether it is moving or still water, the nature of the bottom, etc. Finally, Möbius states that the sexual glands, which form the greater part of the mantle, are white in the male and yellow in the female. However, it has been shown later by Schmidtmann and

VIRCHOW that edible mussels may become poisonous if left in filthy water for fourteen days or longer, and, on the other hand, poisonous ones may become fit for food if kept for four weeks in good water.

Cats and dogs which have eaten voluntarily of poisonous mussels have suffered from symptoms similar to those observed in man; and rabbits have been poisoned by the administration of the water in which the food has been cooked. A rabbit which was treated in this manner by SCHMIDTMANN died within one minute. From these mussels BRIEGER extracted the ptomaine mytilotoxine, which will be discussed in a subsequent chapter. This poison has a curare-like action. Whether or not those mussels which produce other symptoms also contain ptomaines, remains for future investigations to determine.

In 1887 three other cases of mussel poisoning, one fatal case, occurred at Wilhelmshaven, the place which supplied BRIEGER with the mussels from which he obtained mytilotoxine. SCHMIDTMANN has found that non-poisonous mussels placed in the waters of this bay soon become poisonous, and that the poisonous mussels from the bay placed in the open sea soon lose their poisonous properties. LINDER has found in the water of the bay and in the mussels living in it a great variety of protozoa, amœba, bacteria, and other lower organisms, which are not found in the water of the open sea nor in the non-poisonous mussel. He has also found that, if the water of the bay be filtered, non-poisonous mussels in it do not become poisonous. He therefore concludes that poisonous mussels are those which are suffering from disease due to residence in filthy water.

BRIEGER has tested dead and decomposed mussels taken from the open sea for mytilotoxine, with negative results.

Poisonous Oysters and Eels.—Pasquier reported cases of poisoning at Havre from the eating of oysters taken from an artificial bed which had been established near the outlet of a drain from a public water-closet. Christison says that an "unusual prevalence of colic, diarrhœa, and cholera" at Dunkirk was believed to have been traced to an importation of unwholesome oysters from the Normandy coast. Vaughan and Novy obtained tests for tyrotoxicon in the liquor of some decomposed oysters which had caused illness in many people at a church festival.

Virey states that many persons were attacked with violent pain and diarrhœa a few hours after eating a paté made of eels from a stagnant cattle-ditch near Orleans, also that similar cases have occurred in various parts of France, and that domestic animals have been killed by eating the remains of the poisonous dish.

Sausage Poisoning.—This is also known as botulismus and allantiasis. While considerable diversity has been observed in symptoms of sausage poisoning, we cannot divide the cases into classes from their symptomatology as has been done in mussel poisoning. The first effects may manifest themselves at any time from one hour to twenty-four hours after eating of the sausage, and cases are recorded in which, it is stated, no symptoms appeared until several days had passed. However, we must remember that trichinosis was frequently, in former times, classed as sausage poisoning, and it is highly probable that these cases of long delay in the appearance of the symptoms were really not due to putrefaction, but to the presence of parasites in the meat. A large majority of the one hundred and twenty-four cases more recently reported by Müller sickened within twenty-four hours, and out of

the forty-eight of these which were fatal, six died within the first twenty-four hours. At first there is dryness of the mouth, constriction of the throat, uneasiness in the stomach, nausea, vomiting, vertigo, indistinctness of vision, dilatation of the pupils, difficulty in swallowing, and usually diarrhœa, though obstinate constipation may exist from the first. There is, as a rule, a sensation of suffocation, and the breathing becomes labored. The pulse is small, thready, and rapid. In some cases the radial pulse may be imperceptible. Marked nervous prostration and muscular debility follow. These symptoms vary greatly in prominence in individual cases. The retching and vomiting, which may be most distressing and persistent in some instances, in others are trivial at the beginning and soon cease altogether. The same is true of the diarrhœa. As a rule, the functions of the brain proceed normally, but there may be delirium, then coma and death. In some there are marked convulsive movements, especially of the limbs, in others, paralysis may be an early and marked symptom. The pupils may dilate, then become normal and again dilate. There is frequently ptosis, and paralysis of the muscles of accommodation is not rare. Complete blindness has followed in a few instances.

The fatality varies greatly in different outbreaks. In 1820 KERNER collected reports of seventy-six cases, of which thirty-seven were fatal. In his next publication (1822) he increased the number to one hundred and fifty-five cases, with eighty-four fatal results. This gave a mortality of over fifty per cent., while in one outbreak reported by MÜLLER the mortality was less than two per cent.

A large proportion of the cases of sausage poisoning have occurred in Würtemberg and the immediately adja-

cent portions of Baden. This fact has, without doubt, been correctly ascribed to the methods there practised of preparing and curing the sausage. It is said to be common for the people to use the blood of the sheep, ox, and goat in the preparation of this article of diet. Moreover, the blood is kept sometimes for days in wooden boxes and at a high temperature before it is used. In these cases it is altogether likely that putrefaction progresses to the poisonous stage before the process of curing is begun. However, cases of poisoning have occurred from beef and pork sausages as well.

Moreover, the method of curing employed in Würtemberg favors putrefaction. A kind of sausage known as "blunzen" is made by filling the stomachs of hogs with the meat. In curing, the interior of this great mass is not acted upon, and putrefaction sets in. The curing is usually done by hanging the sausage in the chimney. At night the fire often goes out and the meat freezes. The alternate freezing and thawing render decomposition more easy. The interior of the sausage is generally the most poisonous. Indeed, in many instances those who have eaten of the outer portion have been unharmed; while those who have eaten of the interior of the same sausage have been most seriously affected.

Many German writers state that when a poisonous sausage is cut, the putrid portion has a dirty, grayish-green color, and a soft, smeary consistency. A disagreeable odor, resembling that of putrid cheese, is perceptible. The taste is unpleasant, and sometimes a smarting of the mouth and throat is produced. Post-mortem examination after sausage poisoning shows no characteristic lesion. It is generally stated that putrefaction sets in very tardily, but MÜLLER shows that no reliance can be placed upon this

point, and states that out of forty-eight recorded autopsies, it was especially stated in eleven that putrefaction rapidly developed. In some instances there has been noticed hyperæmia of the stomach and intestinal canal, but this is by no means constant. The liver and brain have been reported as congested, but this would result from the failure of the heart, and would, by no means, be characteristic of poisoning with sausage.

Von Faber, in 1821, observed sixteen persons who were made sick by eating fresh, unsmoked sausage made from the flesh of a pig which had suffered from an abscess on the neck. Five of the patients died. The symptoms were as follows: There was a constriction of the throat, difficulty in swallowing, retching, vomiting, colic-like pains, vertigo, hoarseness, dimness of vision, and headache. Later and in severer cases, there was complete exhaustion, and, finally, paralysis. The eyeballs were retracted, the pupils were sometimes dilated, then contracted; they did not respond to light; there was paralysis of the upper lids. The tonsils were swollen, but not as in tonsillitis. Liquids which were not irritating could be carried as far as the œsophagus, when they were then ejected from the mouth and nose with coughing. Solid foods could not be swallowed at all. On the back of the tongue and in the pharynx there was observed a puriform exudate.

Obstinate constipation existed in all, while the sphincter ani was paralyzed. The breathing was easy, but all had a croupous cough. The skin was dry. There was incontinence of urine. There was no delirium and the mind remained clear to the last.

Post-mortem examinations were held on four. The skin was rough—"goose-skin." The abdomen was retracted. The large vessels in the upper part of the stomach were

filled with black blood. The contents of the stomach consisted of a reddish-brown, semi-fluid substance, which gave off a repugnant, acid odor. In one case the omentum was found greatly congested. The large intestine was very pale, and the right ventricle of the heart was filled with dark fluid blood.

SCHUZ cites thirteen cases of poisoning from liver sausage in which the symptoms differed from the foregoing in the following respects:

(1) In only one out of the thirteen was there constipation; all the others had numerous watery, typhoid-like stools.

(2) Symptoms involving the sense of sight were present in only three; in all the pupils were unchanged.

(3) The croupous cough was wholly wanting; though in many there was complete loss of voice. Difficulty of swallowing was complained of by only one.

(4) Delirium was marked in all; and in one the disturbance of the mental faculties was prominent for several weeks.

(5) There were no deaths.

(6) The time between eating the sausage and the appearance of the symptoms varied from eighteen to twenty-four hours, and the duration of sickness from one to four weeks; though in one case complete recovery did not occur until after two and one-half months.

The sausages were not smoked, and all observed a garlic odor, though no garlic had been added to the meat.

TRIPE reports sixty-four cases. The symptoms came on from three and one-half to thirty-six hours after eating. The stools were frequent, watery, and of offensive odor. In some there was delirium. One died. In the fatal case the hands and face were cold and swollen. The pulse was

rapid and weak. The pupils were contracted, but responded to light. The small intestine was found inflamed.

HEDINGER reports the case of a man and a woman with the usual symptoms, but during recovery the dilatation of the pupils was followed by contraction. Birds ate of this sausage, and were not affected.

RÖSER reports cases in which there were found, after death, abscesses of the tonsils, a dark, bluish appearance of the mucous membrane of the pharynx, larynx, and bronchial tubes, dark redness of the fundus of the stomach, and circumscribed, gray, red, and black spots on the mucous membrane of the intestine. The liver was brittle, and the spleen enlarged.

Many theories concerning the nature of the active principle of poisonous sausage have been advanced. It was once believed to consist of pyroligneous acid, which was supposed to be absorbed by the meat from the smoke used in curing it; but it was soon found that unsmoked sausage might be poisonous also. EMMERT believed that the active agent was hydrocyanic acid, and JÄGER'S theory supposed the presence of picric acid. But these acids are not found in poisonous sausage, and, moreover, their toxicological effects are wholly unlike those observed in sausage poisoning. As we have elsewhere seen, KERNER believed that he had found the poisonous principle in a fatty acid. This theory was supported by DANN, BÜCHNER, and SCHUMANN. KERNER believed the poison to consist of either caseic or sebacic acid, or both, while BUCHNER named it acidum botulinicum; but the acids of the former proved to be inert, and that of the latter to have no existence. SCHLOSSBERGER first suggested that the poisonous substance is most probably basic in character, and he found an odoriferous, ammoniacal base which could not be found in good sausage,

and which did not correspond to any known amides, imides, or nitril bases. However, this substance has not been obtained by any one else, nor has it been demonstrated to be poisonous.

LIEBIG, DUFLAS, HIRSCH, and SIMON believed in the presence of a poisonous ferment. VAN DEN CORPUT described sarcina botulina, which was believed to constitute the active agent. MÜLLER, HOPPE-SEYLER, and others have found various microörganisms, and VIRCHOW, EICHENBERG, and others have examined microscopically the blood of persons poisoned with sausage. Recently, EHRENBERG has attempted to isolate the poisonous substance by employing BRIEGER'S method, but he obtained only inert substances.

In the light of the knowledge of to-day concerning the nature of putrefaction, there can scarcely be a doubt that the active agent of poisonous sausage consists of an easily decomposable base, and we predict its isolation in the very near future.

POISONOUS HAM.—Under this head, we shall not discuss cases of poisoning from trichina or other parasites, but shall refer only to those instances in which the toxic agent has originated in putrefactive changes. A number of such cases have been observed within the past ten years, but only a few of them have been investigated scientifically. The best known of these, as well as the most thoroughly studied, is the Wellbeck poisoning, which BALLARD investigated successfully. In June, 1880, a large number of persons attended a sale of timber and machinery on the estate of the Duke of Portland, at Wellbeck. The sale continued four days, and lunches were served by the proprietress of a neighboring hotel. The refreshments consisted of cold,

boiled ham, cold, boiled, or roasted beef, cold beefsteak pie, mustard and salt, bread and cheese, pickles, and Chutney sauce. The drinks were bottle and draught beer, spirits, ginger beer, lemonade, and water. Many were poisoned, and BALLARD obtained the particulars of seventy-two cases, among which there were four deaths. The symptoms are given by BALLARD as follows:

"I propose to speak of the attacks under the name of 'diarrhœal illness,' because diarrhœa was the most constant of all the symptoms observed, and the other symptoms were in some respects so peculiar that I am indisposed to give to the disease any name otherwise generally recognized. As might have been anticipated from our experience of diseases in general, there were varieties in severity among the cases investigated; and symptoms strongly marked in some, were slightly marked or altogether wanting in others. Perhaps I shall do the best service by giving first a general sketch of the course of the illness, subsequently illustrating it by a description of a few well-marked cases.

"A period of incubation preceded the illness. In fifty-one cases where this could be accurately determined, it was twelve hours or less in five cases; between twelve and thirty-six hours in thirty-four cases; between thirty-six and forty-eight hours in eight cases; and later than this in only four cases. In many cases the first definite symptoms occurred suddenly, and evidently unexpectedly, but in some cases there were observed during the incubation more or less feeling of languor and ill health, loss of appetite, nausea, or fugitive, griping pains in the belly. In about a third of the cases, the first definite symptom was a sense of chilliness usually with rigors, of trembling, in one case accompanied by dyspnœa; in a few cases it was giddiness with faintness, sometimes accompanied by a cold sweat and

tottering; in others, the first symptom was headache or pain somewhere in the trunk of the body—*e. g.*, in the chest, back, between the shoulders, or in the abdomen, to which part the pain, wherever it might have commenced, subsequently extended. In one case the first symptom noticed was a difficulty in swallowing. In two cases it was intense thirst. But however the attack may have commenced, it was usually not long before pain in the abdomen, diarrhœa, and vomiting came on, diarrhœa being of more certain occurrence than vomiting. The pain in several cases commenced in the chest or between the shoulders, and extended first to the upper and then to the lower part of the abdomen. It was usually very severe indeed, quickly producing prostration or faintness, with cold sweats. It was variously described as crampy, burning, tearing, etc. The diarrhœal discharges were in some cases quite unrestrainable, and (where a description of them could be obtained) were said to have been exceedingly offensive and usually of a dark color. Muscular weakness was an early and very remarkable symptom in nearly all the cases, and in many it was so great that the patient could only stand by holding on to something. Headache, sometimes severe, was a common and early symptom; and in most cases there was thirst often intense and most distressing. The tongue, when observed, was described usually as thickly coated with a brown, velvety fur, but red at the tip and edges. In the early stage the skin was often cold to the touch, but afterward fever set in, the temperature rising in some cases to 101°, 103°, and 104°. In a few severe cases where the skin was actually cold, the patient complained of heat, insisted on throwing off the bedclothes, and was very restless. The pulse in the height of the illness became quick, counting in some cases 100 to 128. The above

were the symptoms most frequently noted. Other symptoms occurred, however, some in a few cases, and some only in solitary cases. These I now proceed to enumerate. Excessive sweating, cramps in the legs, or in both legs and arms, convulsive flexion of the hands or fingers, muscular twitchings of the face, shoulders, or hands, aching pain in the shoulders, joints, or extremities, a sense of stiffness of the joints, prickling or tingling or numbness of the hands lasting far into convalescence in some cases, a sense of general compression of the skin, drowsiness, hallucinations, imperfection of vision, and intolerance of light. In three cases (one, that of a medical man) there was observed yellowness of the skin, either general or confined to the face and eyes. In one case, at a late stage of the illness, there was some pulmonary congestion, and an attack of what was regarded as gout. In the fatal cases, death was preceded by collapse like that of cholera, coldness of the surface, pinched features and blueness of the fingers and toes, and around the sunken eyes. The debility of convalescence was in nearly all cases protracted to several weeks.

"The mildest cases were characterized usually by little remarkable beyond the following symptoms, viz., abdominal pains, vomiting, diarrhœa, thirst, headache, and muscular weakness; any one or two of which might be absent."

The cause of this illness was traced conclusively to the hams eaten. KLEIN found in the meat a bacillus, cultures of which were used for inoculating animals. These inoculations were found generally to be followed by pneumonia. No attempt was made to isolate a ptomaine.

Later, BALLARD reported fifteen cases with symptoms similar to the above, and with one death, from eating baked pork. Not all of those who ate of this pork were made sick. This might have been due to inequality in the putre-

factive changes in different portions of the meat, or it may have been due to differences in temperature in various portions of the meat during the cooking. In the blood, pericardial fluid, and lungs of the fatal case, KLEIN observed bacilli similar to those discovered in the Wellbeck inquiry. Pneumonia was produced by inoculating guinea-pigs and mice with these bacilli.

August 29, 1887, 256 soldiers and 36 citizens at Middleburg, Holland, were taken sick after eating meat from a cow which had been killed while suffering from puerperal fever. The symptoms were nausea, vomiting, purging, elevation of temperature, and prostration. In some there were observed dizziness, sleepiness, and dilatation of the pupil. After a few days these symptoms gradually disappeared, and in many an eczematous eruption of the lips gave annoyance. Pigs, cats, and dogs, which ate of the offal of this animal, were also made sick. Thorough cooking did not destroy the poison, and those who took soup and bouillon made from the meat were affected like those who ate of the muscular fibre. In most of the cases the symptoms came on within twelve hours after eating the meat.

On a fête-day at Zurich, in 1839, 600 persons who were fed upon cold veal and ham were taken ill, with shivering, giddiness, vomiting, and diarrhœa. Some were delirious and others were salivated, the saliva being extremely fetid. In the worst cases, there were involuntary stools, collapse, and death. The cause was traced to putrefactive changes in the meat.

SIEDLER reports an instance of four persons having been made sick by eating decomposed goose-grease. There were giddiness, prostration, and violent vomiting. No metallic poison could be found. The grease was rancid, of repul-

sive odor, and three ounces of it given to a dog produced the same symptoms which had been observed in the persons.

CHRISTISON reports a number of cases in which persons were seriously, a few fatally, affected by eating various kinds of meat which had undergone partial putrefaction.

OLLIVIER found six persons poisoned, four of them fatally, by eating of decomposed mutton. He also mentions the poisoning of a family of three with ham pie. Chemical analysis failed to reveal the presence of any poison.

BOUTIGNY, having failed to find any poison in the meat furnished at a festival, and to which the serious illness of many was attributed, made a meal of stuffed turkey furnished by the same dealer, but after a short time his countenance became livid, his pulse small and feeble, a cold sweat bathed his body, and violent vomiting and purging followed. His recovery was slow.

GEISELER observed nausea, vomiting, purging, and delirium after eating of bacon which was imperfectly cured.

POISONOUS CANNED MEATS.—Cases of poisoning from eating canned meats have become quite frequent. Although it may be possible that in some instances the untoward effects result from metallic poisoning, in the great majority of cases the poisonous principles are formed by putrefactive changes. In many instances it is probable that decomposition begins after the can is opened by the consumer. In others, the canning is carelessly done and putrefaction is far advanced before the food reaches the consumer. In still other instances, the meat may be taken from diseased animals, or it may undergo putrefactive changes before

the canning. What is true of canned meats is also true of canned fruits and vegetables.

Dr. ASHWORTH, of Smithland, Iowa, has reported to us three fatal cases of poisoning from canned apricots. An infant, which was only eight days old, and which must have received the poison from its mother's breast, died within a few hours. The mother died forty-three hours after eating the apricots, and the father on the sixth day. The symptoms corresponded with those of poisoning by tyrotoxicon. However, it seems that no analysis was made, and these may have been cases of mineral poisoning.

POISONOUS CHEESE.—In 1827 HÜNNEFELD made some analyses of poisonous cheese, and experimented with extracts upon the lower animals He accepted the ideas of KERNER in regard to poisonous sausage in a somewhat modified form, and thought the active agents to be sebacic and caseic acids. About the same time, SERTÜRNER, making analyses of poisonous cheese for WESTRUMB, also traced the poisonous principles, as he supposed, to these fatty acids. We see from this that during the first part of the present century the fatty acid theory, as it may be called, was generally accepted.

In 1848, CHRISTISON, after referring to the work of HÜNNEFELD and SERTÜRNER, made the following statement: "His (Hünnefeld's) experiments, however, are not quite conclusive of the fact that these fatty acids are really the poisonous principles, as he has not extended his experimental researches to the caseic and sebacic acids prepared in the ordinary way. His views will probably be altered and simplified if future experiments should confirm the late inquiries of BRACONNOT, who has stated that PROUST'S

caseic acid is a modification of acetic acid combined with an acrid oil."

In 1852 SCHLOSSBERGER made experiments with the pure fatty acids and demonstrated their freedom from poisonous properties. These experiments have been verified repeatedly, so that now it is well known that all the fatty acids obtainable from cheese are devoid of poisonous properties.

It may be remarked here, that there is every probability that the poisonous substance was present in the extracts obtained by the older chemists. Indeed, we may say that this is a certainty, since the administration of these extracts to cats was, in some instances at least, followed by fatal results. The great mass of these extracts consisted of fatty acids, and as the chemists could find nothing else present, they very naturally concluded that the fatty acids themselves constituted the poisonous substance.

Since the overthrow of the fatty acid theory, various conjectures have been made, but none of them is worthy of consideration.

We make the following quotations from some of the best authorities who wrote during the first half of the present decade upon this subject:

HILLER says: "Nothing definite is known of the nature of cheese poison. Its solubility seems established from an observation by HUSEMANN, a case in which the poison was transmitted from a nursing mother to her child."

HUSEMANN wrote as follows: "The older investigations of the chemical nature of cheese poison, which led to the belief of putrefactive cheese acids and other problematic substances, are void of all trustworthiness, and the discovery of the active principle of poisonous cheese may not be looked for in the near future, on account of the proper

animals for controlling the experiments with the extracts, as dogs can eat large quantities of poisonous cheese without its producing any effect."

BRIEGER stated in 1885: "All kinds of conjectures concerning the nature of this poison have been formed, but all are even devoid of historical interest; because they are not based upon experimental investigations. My own experiments toward solving this question have not progressed very far."

In the above quotation we think that BRIEGER has hardly done justice to the work of HÜNNEFELD and SERTÜRNER. Their labors can hardly be said to be wholly devoid of historical interest, and they certainly did employ the experimental method of inquiry. We shall soon see as to the correctness of the prediction of HUSEMANN as given above.

In the years 1883 and 1884 there were reported to the Michigan State Board of Health about three hundred cases of cheese poisoning. As a rule, the first symptoms appeared within from two to four hours after eating the cheese. In a few the symptoms were delayed from eight to ten hours and were very slight. The attending physicians reported that the gravity of the symptoms varied with the amount of cheese eaten, but no one who ate of the poisonous cheese wholly escaped. One physician reported the following symptoms: "Every one who ate of the cheese was taken with vomiting, at first of a thin, watery, later a more consistent reddish colored substance. At the same time the patient suffered from diarrhœa with watery stools. Some complained of pain in the region of the stomach. At first the tongue was white, but later it became red and dry, the pulse was feeble and irregular; countenance pale, with marked cyanosis. One small boy, whose condition seemed

very critical, was covered all over the body with bluish spots."

Dryness and constriction of the throat were complained of by all. In a few cases the vomiting and diarrhœa were followed by marked nervous prostration, and in some dilatation of the pupils was observed.

Notwithstanding the severity of the symptoms in many, there was no fatal termination among these cases, though several deaths from cheese poisoning in other outbreaks have occurred. Many of the physicians at first diagnosed the cases from the symptoms as due to arsenical poisoning, and on this supposition some administered ferric hydrate. Others gave alcohol and other stimulants and treated upon the expectant plan.

VAUGHAN, to whom the cheese was sent for analysis, made the following report: "All of these three hundred cases were caused by eating of twelve different cheeses. Of these, nine were made at one factory, and one each at three other factories. Of each of the twelve I received smaller or larger pieces. Of each of ten I received only small amounts. Of each of the other two I received about eighteen kilograms. The cheese was in good condition and there was nothing in the taste or odor to excite suspicion. However, from a freshly cut surface there exuded numerous drops of a slightly opalescent fluid which reddened litmus paper instantly and intensely. Although, as I have stated, I could discern nothing peculiar in the odor, if two samples, one of good, the other of poisonous cheese, were placed before a dog or cat, the animal would invariably select the good cheese. But if only poisonous cheese was offered, and the animal was hungry, it would partake freely. A cat was kept seven days and furnished only poisonous cheese and water. It ate freely of the cheese

and manifested no untoward symptoms. After the seven days the animal was etherized and abdominal section was made. Nothing abnormal could be found. I predicted, however, in one of my first articles on poisonous cheese, that the isolated poison would affect the lower animals. As to the truth of this prediction we will see later.

"My friend, Dr. STERNBERG, the eminent bacteriologist, found in the opalescent drops above referred to, numerous micrococci. But inoculations of rabbits with these failed to produce any results.

"At first I made an alcoholic extract of the cheese. After the alcohol was evaporated in vacuo at a low temperature, a residue consisting mainly of fatty acids remained. I ate a small bit of this residue, and found that it produced dryness of the throat, nausea, vomiting, and diarrhœa. The mass of this extract consisted of fats and fatty acids, and for some weeks I endeavored to extract the poison from these fats, but all attempts were unsuccessful. I then made an aqueous extract of the cheese, filtered this and drinking some of it, found that it also was poisonous. But after evaporating the aqueous extract to dryness on the water-bath at 100°, the residue thus obtained was not poisonous. From this I ascertained that the poison was decomposed or volatilized at or below the boiling point of water. I then tried distillation at a low temperature, but by this the poison seemed to be decomposed.

"Finally, I made the clear, filtered aqueous extract, which was highly acid, alkaline with sodium hydrate, agitated this with ether, removed the ether, and allowed it to evaporate spontaneously. The residue was highly poisonous. By resolution in water and extraction with ether, the poison was separated from foreign substances. As the ether took up some water, this residue consisted of an aqueous

solution of the poison. After this was allowed to stand for some hours in vacuo over sulphuric acid, the poison separated in needle-shaped crystals. From some samples the poison crystallized from the first evaporation of the ether, and without standing in vacuo. This happened only when the cheese contained a comparatively large amount of the poison. Ordinarily, the microscope was necessary to detect the crystalline shape. From sixteen kilograms of one cheese, I obtained about 0.5 gram of the poison, and in this case the individual crystals were plainly visible to the unaided eye. From the same amount of another cheese, I obtained only about 0.1 gram, and the crystals in this case were not so large. I have no idea, however, that by the method used all the poison was separated from the cheese."

To this ptomaine VAUGHAN has given the name tyrotoxicon (τυρόσ, cheese, and τοξικον, poison). Its chemistry will be discussed in a subsequent chapter.

During 1887, WALLACE found tyrotoxicon in two samples of cheese which had caused serious illness. The first of these came from Jeanesville, Pa., and the symptoms as reported to WALLACE by DOOLITTLE, who had charge of the cases, were as follows: "There were at least fifty persons poisoned by this cheese. There were also eight others who ate of the cheese, but felt no unpleasant effects; whether this was due to personal idiosyncrasy, or to an uneven distribution of the poison throughout the cheese, I am unable to say.

"The majority, however, comprising fifty or sixty persons, were seized, in from two to four hours after eating the cheese, with vertigo, nausea, vomiting, and severe rigors, though varying in their order of appearance and in severity in different cases. The vomiting and chills were the most constant and severe symptoms in all the cases, and were

soon followed by severe pain in the epigastric region, cramps in the feet and lower limbs, purging and griping pain in the bowels, a sensation of numbness or pins and needles, especially in the limbs, and lastly, very marked prostration, amounting almost to collapse in a few cases.

"The vomit at first consisted of the contents of the stomach, and had a strong odor of cheese; afterward it consisted of mucus, bile, and in three or four of the severer cases blood was mixed with the mucus in small quantities. Microscopic examination of the same was not made, but to the eye it appeared as such. The vomiting and diarrhœa lasted from two to twelve hours; the rigors and muscular cramps, one to two hours. The diarrhœal discharges, at first fæcal, became later watery and light colored. No deaths occurred, and for the most part the effects were transient, and all that remained on the following day were the prostration and numbness; the latter occurred in about one-half the cases, and disappeared in from one to three days.

"Children, as a rule, seemed to suffer less than adults, and, of course, it was not possible to elicit as definite symptoms from them. The suddenness of the attack was remarked by all, some feeling perfectly well until the moment of attack. Nor did the symptoms seem to be in proportion to the amount of cheese taken; some of the severest cases declared they had not eaten more than a cubic inch of it. One of the severest cases was about six and one-half months pregnant, but no interference with pregnancy occurred. All the cheese which caused the sickness came from the same piece."

The second sample of cheese examined by WALLACE came from Riverton, N. J. This outbreak included a smaller number of persons, all of whom recovered.

Still more recently WOLFF has detected tyrotoxicon in cheese which poisoned several persons at Shamokin, Pa. The pores of this cheese were found filled with a grayish-green fungoid growth, though it is not supposed that this fungus was connected in any way with the poisonous nature of the cheese. Tests were made for mineral poison with negative results, after which tyrotoxicon was recognized both by chemical and physiological tests. "A few drops of the liquid (extract), placed on the tongue of a young kitten, produced prompt emesis and numerous watery dejections with evident depression and malaise of the animal. A larger cat was similarly affected by it, though the depression and malaise were not so marked nor so long continued."

Cheese poisoning caused the death of several children in the neighborhood of Heiligenstadt, in 1879, and there were many fatal cases from the same cause in Pyrmont, in 1878. Unfortunately we have not been able to find any detailed account of either the symptoms or the post-mortem appearances in these cases.

EHRHART has recently published the history of some cases of poisoning from cheese, of which the following is an abstract: The family of a workman, consisting of eight persons, ate for supper 600 grams (about eighteen ounces) of Limburger cheese. The rind was covered with a heavy mould, while the interior had become fluid from putrefaction, and was of bitter taste. Three ate only of the mouldy rind, and these remained well. The next morning, the five who had eaten of the inner portion suffered from vertigo, nausea, vomiting, and abdominal pains; no stool. The father had convulsive movements of all the extremities. The pupils were dilated, and did not respond to light; there were double vision, cold sweat, skin cyanotic, abdomen distended, difficulty in swallowing, delirium, mild trismus,

and temperature 40° C. (104° F.). The temperature of the mother, on account of the great collapse, was subnormal. She had no convulsive movements, but there was prolonged loss of consciousness. The pulse was small and thready, and threatened paralysis of the heart. Recovery was very slow. The others suffered only from gastro-enteric symptoms. EHRHART discusses the question as to whether these symptoms were due to tyrotoxicon, or to infection with microörganisms; but as we have not had access to his original paper, we do not know what his conclusions are. However, there cannot be much doubt that in those cases in which the organism is taken into the alimentary canal, it continues the elaboration of its poisonous products.

POISONOUS MILK.—In 1885 VAUGHAN found tyrotoxicon in milk which had stood in a well-stoppered bottle for about six months. It was presumed that this milk was, when first obtained, normal in composition, but since this was not known with certainty, the following experiments were made: Several gallon bottles were filled with normal milk, tightly closed with glass stoppers, and allowed to stand at the ordinary temperature of the room. From time to time a bottle was opened and the test for tyrotoxicon was made. These tests were followed by negative results until about three months after the experiment was begun. Then the poison was obtained from one of the bottles. The coagulated milk was filtered through paper. The filtrate, which was colorless and decidedly acid in reaction, was rendered feebly alkaline by the addition of potassium hydrate and agitated with ether. After separation, the ethereal layer was removed with a pipette, passed through a dry filter paper in order to remove a flocculent, white substance which floated in it, and then allowed to evaporate spontaneously.

If necessary, this residue was dissolved in water and again extracted with ether. As the ether takes up some water, there is usually enough of the latter left after the spontaneous evaporation of the ether to hold the poison in solution, and in order to obtain the crystals this aqueous solution must be allowed to stand for some hours in vacuo over sulphuric acid.

From one-half gallon of the milk there was obtained quite a concentrated aqueous solution of the poison after the spontaneous evaporation of the ether. Ten drops of this solution placed in the mouth of a small dog three weeks old, caused within a few minutes frothing at the mouth, retching, the vomiting of frothy fluid, muscular spasm over the abdomen, and after some hours watery stools. The next day the dog seemed to have partially recovered, but was unable to retain any food. This condition continuing for two or three days the animal was killed with chloroform. No examination of the stomach was made.

In 1886 NEWTON and WALLACE obtained tyrotoxicon from milk, and studied the conditions under which it forms. Their report is of so much value that the greater part of it is herewith inserted.

"On August 7th twenty-four persons, at one of the hotels at Long Branch, were taken ill soon after supper. At another hotel, on the same evening, nineteen persons were seized with the same form of sickness. From one to four hours elapsed between the meal and the first symptoms. The symptoms noticed were those of gastro-intestinal irritation, similar to poisoning by any irritating material—that is, nausea, vomiting, cramps, and collapse; a few had diarrhœa. Dryness of the throat and a burning sensation in the œsophagus were prominent symptoms.

"While the cause of the sickness was being sought for, and one week after the first series of cases, thirty persons at another hotel were taken ill with precisely the same symptoms as noticed in the first outbreak.

"When the news of the outbreak was published one of us immediately set to work, under the authority of the State Board of Health, to ascertain the cause of the illness. The course of the investigation was about as follows:

"The character of the illness indicated, of course, that some article of food was the cause, and the first part of our task was to single out the one substance that seemed at fault. The cooking utensils were also suspected, because unclean copper vessels have often caused irritant poisoning. Articles of food, such as lobsters, crabs, blue fish, and Spanish mackerel, all of which at times, and with some persons very susceptible to gastric irritation have produced toxic symptoms, were looked for, but it was found that none of these had been eaten at the time of the outbreak. The cooking vessels were examined, and all were found clean and bright, and no evidence of corrosion was presented.

"Further inquiry revealed the fact that all who had been taken ill had used milk in greater or less quantities, and that persons who had not partaken of milk escaped entirely; corroborative of this, it was ascertained that those who had used milk to the exclusion of all other food were violently ill. This was prominently noticed in the cases of infants fed from the bottle, when nothing but uncooked milk was used. In one case an adult drank about a quart of the milk, and was almost immediately seized with violent vomiting followed by diarrhœa, and this by collapse. Suffice it to say, that we were able to eliminate all other articles of food and to decide that the milk was the sole cause of the outbreak.

"Having been able to determine this, the next step was to discover why that article should, in these cases, cause so serious a form of sickness.

"The probable causes which we were to investigate were outlined as follows: (1) Some chemical substance, such as borax, boric acid, salicylic acid, sodium bicarbonate, sodium sulphate, added to preserve the milk or to correct acidity. (2) The use of polluted water as an adulterant. (3) Some poisonous material accidentally present in the milk. (4) The use of milk from diseased cattle. (5) Improper feeding of the cattle. (6) The improper care of the milk. (7) The development in the milk of some ferment or ptomaine, such as tyrotoxicon.

"At the time of the first outbreak we were unable, unfortunately, to obtain any of the noxious milk, as that unconsumed had been destroyed; but at the second outbreak a liberal quantity was procured.

"It was soon ascertained that one dealer had supplied all the milk used at the three hotels where the cases of sickness had occurred. His name and address having been obtained, the next step in the investigation was to inspect all the farms, and the cattle thereon, from which the milk was taken. We also learned that two deliveries at the hotels were made daily, one in the morning and one in the evening; that the milk supplied at night was the sole cause of sickness, and that the milk from but one of the farms was at fault. The cows on this farm were found to be in good health, and, besides being at pasture, were well fed with bran, middlings, and corn-meal.

"So far we had been able to eliminate as causes diseased cattle and improper feeding, and we were then compelled to consider the other possible sources of the toxic material.

"While the inspection of the farms was being made, the

analysis of the milk was in progress. The results of this showed that no chemical substance had been added to the milk, that it was of average composition, that no polluted water had been used as a diluent, and that no poisonous metals were present. This result left us nothing to consider but two probable causes: improper care of the milk, and the presence of a ferment.

"As to the former, we soon learned much. The cows were milked at the unusual and abnormal hours of midnight and noon, and the noon's milking—that which alone was followed by illness—was placed while hot, in the cans, and then, without any attempt at cooling, carted eight miles during the warmest part of the day in a very hot month.

"This practice seemed to us sufficient to make the milk unpalatable, if not injurious, for it is well known that when fresh milk is closed up in a tight vessel and then deposited in a warm place, a very disagreeable odor and taste are developed. Old dairymen speak of the animal heat as an entity, the removal of which is necessary in order that the milk shall keep well and have a pleasant taste. While we do not give this thing a name, we are fully convinced that milk should be thoroughly cured by proper chilling and aëration before it is transported any distance or sold for consumption in towns or cities.

"This opinion is based on a study of the methods prevalent among experienced dairymen, who ship large quantities of milk to our great cities. The usual practice is to allow the milk to stand in open vessels, surrounded by ice or cold water, for from eight to twelve hours before transportation, and when placed on the cars it has a temperature of from 50° to 60° F., and is delivered to consumers in a perfectly sweet condition. The city of New York receives about 200,000 gallons each day from the surrounding

country, and much of it brought in by the railroads has been on the cars for a time varying from six to twelve hours, yet we seldom hear of any of this milk undergoing the peculiar form of fermentation set up in the Long Branch milk. We may account for this by assuming that the proper care of the milk after it was taken from the cow, and the low temperature at which it was kept, have prevented the formation of any ferment; this opinion seems to be endorsed by all dairymen and managers of large creameries with whom we have consulted. They all agree in stating that milk maintained at a low temperature can be kept sweet and in good condition for many days.

"We have dwelt on this branch of our topic somewhat extensively, because we are fully persuaded that the improper care of the milk had much to do with the illness it produced.

"The results of our inquiry having revealed so much, we next attempted to isolate some substance from the poisonous milk, in order that the proof might be more evident. A quantity of the milk that had caused sickness in the second outbreak was allowed to coagulate, was then thrown on a coarse filter, and the filtrate collected. This latter was highly acid, and was made slightly alkaline by the addition of potassium hydrate. This alkaline filtrate was now agitated with an equal volume of pure, dry ether, and allowed to stand for several hours, when the ethereal layer was drawn off by means of a pipette. Fresh ether was added to the residuum, then agitated, and, when separated, was drawn off and added to the first ethereal extract. This was now allowed to evaporate spontaneously, and the residue, which seemed to contain a small amount of fat, was treated with distilled water and filtered, the filtrate treated with ether, the ethereal solution drawn off

and allowed to evaporate, when we obtained a mass of needle-shaped crystals. This crystalline substance gave a blue color with potassium ferricyanide and ferric chloride, and reduced iodic acid. The crystals, when placed on the tongue, gave a burning sensation. A portion of the crystals was mixed with milk and fed to a cat, when, in the course of half an hour, the animal was seized with retching and vomiting, and was soon in a condition of collapse, from which it recovered in a few hours.

"We are justified in assuming, after weighing well all the facts ascertained in the investigation, that the sickness at Long Branch was caused by poisonous milk, and that the toxic material was tyrotoxicon.

"The production of this substance was no doubt due to the improper management of the milk—that is, too long a time was allowed to elapse between the milking and the cooling of the milk, the latter not being attended to until the milk was delivered to the hotel; whereas, if the milk had been cooled immediately after it was drawn from the cows, fermentation would not have ensued, and the resulting material, tyrotoxicon, would not have been produced."

In the same year, SCHEARER found the same poison in the milk used by, and the vomited matter of, persons made sick at a hotel at Corning, Iowa.

In 1887, FIRTH, an English army surgeon stationed in India, reported an outbreak of milk poisoning among the soldiers of his garrison. From the milk he separated, by VAUGHAN'S method, tyrotoxicon. He also obtained tyrotoxicon from milk which had been kept for some months in stoppered bottles, as had been previously done by Vaughan. (See page 60.)

In 1887, MESIC and VAUGHAN observed four cases of milk poisoning, three of which terminated fatally, and

NOVY and VAUGHAN obtained tyrotoxicon from the milk, and from the contents of the intestine in one of the fatal cases. VAUGHAN reports these cases as follows :

"September 23, 1887, I was visited by Dr. A. G. Mesic, of Milan, Michigan, who informed me that he had four members of a family under his charge, all of whom were seriously ill with peculiar symptoms which he believed to be caused by tyrotoxicon. Since Dr. Mesic has written out for me the history of these cases, I will insert his report in full, as follows :

"'Saturday, September 17, while passing the residence of S. H. Evans, a respectable farmer, I was called in to see him. I found him—a man of about fifty years, spare and muscular—vomiting severely, with flushed face, but with a temperature of 96° F. There was marked throbbing of the abdominal aorta ; the tongue had a white, heavy coating, and the breathing was very labored. I set to work with the ordinary remedies to allay the vomiting, which had already continued for some hours. The vomited matters were colored with bile. Pupils were dilated, and a rash resembling that of scarlatina, but coarser, covered the chest, forearms, and legs below the knees, while the abdomen and thighs remained unaffected. As the bowels had not been moved since the beginning of the attack, I administered a purgative dose of calomel with a little podophyllin and rhubarb. On Sunday a small stool resulted. During that day and night, and the following day, the retching and vomiting continued. Small doses of carbolic acid seemed to give the most relief. After the movement of the bowels the symptoms were somewhat more promising ; but a heavy and unfavorable stupor was observable and persistent.

"'On Sunday the coating of the tongue remained very

thick, and had changed to a dark brown color. At first I thought that his symptoms indicated a depressed condition, which I had known in one instance to precede typhoid fever. However, after a few days, I concluded that I must look for the cause of the condition among the poisons; but I could think of no one poison which would be likely to produce all the symptoms observed. During Monday, Tuesday, and Wednesday, there was but little change, and the treatment was continued.

"'On Thursday morning I found the son Arthur, a lad of eighteen years, strong and vigorous, suffering with the same symptoms, only in a more violent form. After supper on Wednesday evening, he was taken with nausea and vomiting. He had no rash, but the symptoms were otherwise identical with those of the father, except in being more severe. I gave a cathartic, which acted only slightly.

"'At my evening visit I found Mrs. Evans, a lady of about forty-five, previously in good health, with the same symptoms. In this case the stupor was more marked from the first. I was unable at any time to obtain any cathartic action in this case. Copious enemata of warm water were used, but succeeded only in washing some hardened lumps from the rectum. By this time I had concluded that the poison was most likely tyrotoxicon.

"'On Friday morning the only remaining member of the family at home, Miss Alma, sixteen years of age, was affected in the same way as the others. On that day I went to Ann Arbor, and gave a history of the cases so far to Dr. Vaughan, who, from the symptoms, thought that my diagnosis was most probably correct, and he advised with me as to treatment, which I carried out. I gave two grains of sodium salicylate every four hours, and used small doses of the tonics and stimulants, quinine, nux vomica,

digitalis, whiskey, and the aromatic spirits of ammonia. On Saturday the symptoms in all remained unimproved, and in the mother and son the stupor and labored breathing grew more marked.

"'On Sunday, I again went to Ann Arbor, and brought Dr. Vaughan with me to see the patients. The temperature of the mother on Sunday was as low as 94°, and that of the son 95°. Dr. Vaughan agreed with me as to diagnosis and treatment. Sunday evening, the patients were all removed to the house of a neighbor, about forty rods distant (the reasons for this will be given later). Dr. Vaughan and I both expressed the fear that the mother, and possibly the son, would not live through the night. Both of these rapidly grew worse, and the son died at 7.45 A.M., and the mother at 4 P.M., Monday.

"'During Monday the daughter rapidly grew worse, and at the time of her mother's death could not be aroused, and practically she remained unconscious from that time on. The father was very weak, but retained his consciousness all the time. Convulsive movements of the limbs had been noticed in the son, but not in the mother. These now became more marked in the daughter, who remained in the heavy stupor, with labored breathing, until 5 P.M. Thursday, when she died.

"'Mr. Evans has slowly improved, and now, October 18th, is able to walk about the room. The sodium salicylate, even in the small doses used, seemed to cause severe headache; so apparent was this that the drug was discontinued, and drop doses of amyl nitrite, given every hour, seemed to relieve the pain in the head. The father's temperature remained below the normal until Thursday, October 14th, when it reached the normal. After this it was

found once as high as 99.5°, then 99° F., then again normal, where it remains.

"'All complained of a burning constriction in the throat, and difficulty in swallowing, and all, as long as they were conscious, frequently called for ice. In all the pulse was rapid and feeble, and death seemed to result from failure of the heart. Those who died voided urine involuntarily, while Mr. Evans passed small quantities frequently, and for this buchu and uva ursa were given. During his convalescence small doses of morphine were given to the father, as he was unable to sleep, and became very restless. He is now taking teaspoonful doses of the elixir of calisaya and iron every four hours.'

"As stated above by Dr. Mesic, I first saw these patients Sunday, September 25th. On a sofa in the room we found the daughter, Alma. She had been vomiting during the day, and seemed much exhausted. She was not inclined to talk, and seemed to be in a stupor, though when spoken to she responded rationally. Her pupils were slightly dilated, her tongue coated, her pulse 120 and weak, her face flushed, and a violent throbbing could be felt over the abdomen, which was retracted. Her temperature was 96° F.

"In another room were the father, mother, and son, two of them dying. The father was rational, and talked with some freedom when I asked as to the kind of food they had been eating, etc. His pupils were normal. His face could not be said to present any peculiar feature. His pulse was rapid, breathing somewhat labored, and the throbbing of the abdominal aorta was plainly felt. The abdomen was retracted, and there was no pain on pressure. He complained of a burning constriction of the throat, swallowed with difficulty, and said that his throat and stomach felt as though they were on fire.

"The mother lay perfectly still with eyelids closed, as if in a deep sleep. Her pulse was rapid, her face had a livid flush, her breathing was about 35 per minute, and labored. The skin was cool, but neither abnormally moist nor specially dry and harsh. She could not be aroused. In fact, she was comatose.

"The son rolled uneasily from one side of the bed to the other. His breathing, also, was very labored. His eyelids were closed, and the pupils were markedly dilated—did not respond to light. He could not be aroused. In mother and son, as well as in father and daughter, the abdomen was retracted, and the throbbing of the abdominal aorta was easily felt.

"Now, to what were these symptoms due? They were certainly those of some poison. Dr. Mesic had brought me some of the vomited matter, which I tested thoroughly for mineral poisons, with negative results. The symptoms certainly were not those of morphine, strychnine, digitalis, or aconite. They did have some resemblance to those of belladonna, but yet they were not the symptoms of belladonna. The pupils were not as widely dilated as they would be in belladonna poisoning. There was in none of these persons the active delirium of belladonna poisoning. There was no picking at the clothing, no grasping of imaginary objects in the air, no hallucinations of vision. Surely it could not be any vegetable alkaloid with which I was familiar.

"On the other hand, we know that nausea, vomiting, headache, dilatation of the pupil, rapid pulse, heavy breathing, constipation, and great prostration, with stupor, do occur in cases of poisoning with certain ptomaines. Therefore we began to look for conditions which would be favor-

able for the production of putrefactive alkaloids. These conditions we were not long in finding.

"The family, which consisted of the four persons sick, and of a daughter about twenty years of age, who was away from home at the time when the others were taken ill, and for some months before that time, was evidently a tidy one. This was shown by their personal appearance, and by the clothing and bedding. But the house in which they lived was very old, and very much decayed. Mr. Evans had purchased the farm six years ago; and for some three years past, at least, they had been troubled every now and then, one or more of the family, with nausea and vomiting, followed by more or less prostration. But in no instance, up to the present illness, had the symptoms been sufficient to cause them to summon a physician. The family had worked hard in order to pay for the farm, and had determined to make the old house do until they were out of debt. Even before this family had moved to the farm, the house had been known among the neighbors as an unhealthy one, and there had been much sickness and a number of deaths among its former tenants.

"The house is a frame one, and one of the neighbors said to me that it was an old house when he came to the neighborhood thirty-seven years ago. It consists of two rooms on the ground-floor, with attic rooms above. The frame rests upon four large logs or sills, which lie directly upon the ground, and are thoroughly rotten. There is no cellar under any part of the house. From the front, at least, the surface slopes toward the house, and the rain water runs under it. In the floor of one room a trap door had been placed, and directly under this a small excavation had been made for the purpose of collecting the rain water when it accumulated under the house. Although this pit was dry

at the time of our examination, its sides and bottom were marked with cray-fish holes, showing that water had stood in it. The floor was laid of unjointed boards, and every time that it was swept much of the filth fell through the cracks, and every time that the tidy housewife scoured and mopped the floor, the water, carrying with it the filth, ran through the crevices, and thus the conditions most favorable for putrefactive changes were brought into existence and maintained.

"One corner of one of the rooms had been transformed into a small room, or buttery, as it was called, and in this, on shelves, the food was kept. On account of the more frequent scouring demanded by that part of the floor enclosed in this buttery, the boards had rotted away, and a second layer of boards had been placed over the original floor. Between these two floors we found a great mass of moist, decomposing matter, the accumulations of years, which the broom could not reach. When this floor was taken up, a peculiar, nauseating odor was observable, and was sufficient to produce nausea and vomiting in one of the persons engaged in the examination. Some of the dirt from beneath the floor, and some of that which had accumulated between the boards in the buttery, were taken for further study.

"The condition of the house was supposed to be unfavorable to the patients, and for this reason they were moved, as Dr. Mesic has stated, to the house of a neighbor. Of course, thorough examination of the house was not made until the patients had been removed.

"Special inquiry was now made concerning the food used by this family. They had been living very simply. They lived upon bread, butter, milk, and potatoes, with coffee and ripe fruit. They had eaten no canned foods for months.

They ate but little meat. Occasionally a chicken was killed and served, and rarely, some fresh meat was obtained from the village. During the week in which they were taken ill, all the meat used consisted of slices from a piece of bacon, the only meat which was kept in the house, and a chicken. None of the latter remained, but the bacon was examined. It seemed in perfect condition, and contained no trichinæ. Moreover, as has been seen from the history of the cases, all the members of the family were not made sick by any one meal, but the opportunity of obtaining the poison must have been present for some time. Moreover, the fact that previous similar, but less severe, attacks had occurred at intervals for the past three years, convinced us that the poison must owe its origin to some long-existing condition.

"The drinking water supply was also investigated. The water was obtained from a shallow well, and some of it was taken for analysis. But several families had for years used water from this well, and had remained healthy.

"The milk used by the family was studied. Of course, we could get none of that which had been used before the members of the family were stricken down. As soon as he made the diagnosis of tyrotoxicon poisoning, Dr. Mesic ordered the discontinuance of the use of milk, not only with the sick, but he forbade the daughter, who had returned, and any of the visitors using it. Mr. Evans owned four milch cows, and they were supplied with fair pasturage and abundant water. The greater part of the milk was placed in tin cans which were set in a wooden trough in the yard, and surrounded by cold water. The covers to the cans were arranged so that the air could have free access to the milk, and were left in this position until the milk was thoroughly cooled. Indeed, the cans were furnished by a creamery company, which followed the directions which I

have previously given for the care of milk. On his first visit to me, Dr. Mesic brought some of the milk from one of these cans. This I examined, but failed to find tyrotoxicon in it.

"However, the family did not drink any of the milk from the cans. That which they did use was kept in the buttery which I have described. Here it stood upon a shelf, and some members of the family, at least, were in the habit of drinking from it between meals. This was especially true, it is said, of the son. He would frequently come from his work in the fields, go into the buttery and drink a glass or more of the milk. Mr. Evans states that he frequently observed that the taste of the milk was not pleasant. On my first visit to the premises, I advised that some of the milk should be taken from the cans, allowed to stand in the buttery over night, and be sent to me the next day. This was done, and in this milk we found tyrotoxicon, not only by the employment of chemical tests, but by poisoning a kitten with it.

"On the death of the mother and son, Dr. Mesic asked for a post mortem, but the friends objected, and the undertaker used an arsenical embalming fluid, so that, although consent was subsequently obtained, it was decided that the examination would be so vitiated as to be worthless. On the death of the daughter, the coroner summoned a jury, and held an inquest. The post-mortem was conducted by Dr. George A. Hendricks, in the presence of the jury and several physicians who had been invited. Dr. Hendricks has kindly furnished me with his report, which I present here in full:

"The autopsy was held fifteen hours after death. The abdominal viscera were first examined. The great omentum was small, in normal position, covering the small

intestine. The small intestine was moderately distended with flatus. The jejunum was ashy-green in color; the ileum purplish-green. About eighteen inches from the termination of the ileum was found a diverticulum two inches in length. The small intestine contained very little alimentary matter. The vermiform appendix was free, contained some small fecal lumps, and showed no evidence of inflammation. The cæcum, ascending, transverse, and descending colon, were empty and their circular fibres were tightly constricted, except at intervals where the intestine was distended with gas. The sigmoid flexure was moderately distended with gas, and the rectum contained small bits of fecal matter. The stomach was somewhat contracted and lay wholly upon the left side of the median line. It contained a few ounces of fluid. Its extremities were ligated and the organ removed. The mucous membrane of the stomach and intestine were not examined until they reached the chemist. The duodenum was distended with flatus. The liver was normal in size and appearance. The gall-bladder contained about one ounce of bile. The spleen was normal. One-half ounce of fluid deeply stained with blood was found in Douglas's cul-de-sac. The uterus, Fallopian tubes, and ovaries were deeply congested. The left ovary was enlarged and presented on its posterior surface a hemorrhagic spot, oval, about one-half line in length, and several other less distinct ones. The right ovary was normal in size and showed numerous Graaffian scars. The ureters and bladder were normal; the latter contained a small amount of urine. The peritoneum, pancreas, and kidneys were perfectly normal.

"The thoracic cavity was next opened. The lungs were normal; there was about one-half ounce of free serum in the left pleural cavity; none in the right. Pericardium

normal; right auricle in diastole; left auricle and both ventricles in systole.

"The dura mater showed venous congestion; the arachnoid normal; the pia mater congested. On the surface of the centrum ovale, small drops of blood oozed from the divided vessels. The large veins of the velum interpositum were distended. Third and fourth ventricles were slightly distended with serous fluid, but the walls were normal. There seemed to be slight softening of the optic thalami. The sub-arachnoid fluid was about twice the normal quantity.

"On examination of the mucous membrane of the stomach and intestine in the presence of the chemist, Prof. A. B. Prescott, nothing abnormal could be found. The membrane was stained with bile, but there was not the slightest redness. The solitary glands were distinct, but not at all inflamed. Peyer's patches were normal.

"It will be seen that there existed no lesion which would account for the death. The venous congestion observed in the brain would follow from failure of the heart.

"Some of the post-mortem appearances bore a striking resemblance to those which I had observed in cats poisoned with tyrotoxicon. This was especially noticeable in the condition of the mucous membrane of the stomach and intestine. Tyrotoxicon produces the symptoms of a gastro-intestinal irritant, but not the lesions. The contraction of the circular fibres of the intestine, which undoubtedly caused the constipation, I had also observed in cats that died from tyrotoxicon poisoning without either vomiting or stool. The action of this poison upon the stomach and intestine must be through the nervous system. Small doses cause both vomiting and purging, while after large doses vomiting may be impossible, and obstinate constipation may exist. Both

the vomiting and purging after small doses are undoubtedly due in part to increased activity of the circular fibres of the muscular coats, induced through the nerves; and the inability to vomit, and the constipation, one or both of which may be observed after large doses of the poison, are due to spasm of the same muscles, induced in the same manner.

"Prof. A. B. Prescott was requested by the coroner to analyze the material for mineral and vegetable poisons. He made analyses of the stomach and part of its contents, and a portion of the liver. His results were wholly negative.

"Mr. F. G. Novy tested a cold-water extract of the finely divided intestine for ptomaines. The fluid, which was acid in reaction, was filtered, then neutralized with sodium bicarbonate, and shaken with ether. The ether, after separation, was removed, and allowed to evaporate spontaneously. The residue was dissolved in water, and extracted again with ether. This ether residue gave the chemical reactions for tyrotoxicon, and a portion of it was administered to a kitten about two months old. Within half an hour after the administration the kitten began to retch, and soon it vomited. Within the next three hours it was noticed to vomit as many as five times. The breathing became rapid and labored. The animal sat with its head down, and seemed greatly prostrated. The pupils were examined, but could not be said to be dilated. There was no purging. The retching and heavy breathing, with evidences of prostration, continued more or less marked for two days, after which the animal slowly improved.

"A quantity of fresh milk was divided into five portions of one quart each, placed in quart bottles which had been thoroughly cleansed, and treated in the following manner:

"No. 1 consisted of the milk only, and was employed as a control test.

"No. 2 was mixed with a drachm of vomited matter.

"No. 3 was treated with a portion of the contents of the stomach.

"No. 4 was treated with an aqueous extract of the intestine.

"No. 5 was treated with a small portion of the soil which had been taken from the floor of the buttery, stirred up with water.

"These bottles were placed in an air-bath, and kept at a temperature of from 25° to 30° C. for twenty-four hours. Then each was tested for ptomaines. No. 1 yielded no tyrotoxicon, while all of the others contained this poison. The tests were both chemical and physiological. All of the samples yielded a non-poisonous base when treated according to Brieger's method, and the same substance was obtained from perfectly fresh milk. It is most probably formed by the action of the heat and reagents employed in this method. This base was obtained in crystalline form, and several portions of it were administered to kittens without any effect. The further study of this body will be of interest to toxicologists, because it gives many of the general alkaloidal reactions. At first we supposed it to be Brieger's neuridine, and this supposition may still be correct, but, as we obtained it, it gave some reactions which are not given by neuridine, Further investigations will be made on this point.

"Tyrotoxicon was obtained from the filtered milk by two methods: (1) The one which we have previously used, and which consists in neutralizing the filtered milk with sodium bicarbonate, and extracting with ether. That portion of the poison employed in the physiological tests was obtained in this way, and in order to be sure that no poison came

from the ether, the extract from the milk to which nothing had been added was given to a kitten, and was found to produce no effect. (2) The filtrate from the milk was heated to 70° C. (158° F.) (tyrotoxicon decomposes at 91° C. (195.8° F.)) for some minutes, and filtered. This filtrate, which was perfectly clear, was treated with a small quantity of nitric acid in order to convert the tyrotoxicon into a nitrate, then pure potassium hydrate in the solid form was added until the solution was strongly alkaline. This solution was concentrated so far as it could be, on the water-bath. (The potassium compound of tyrotoxicon is not decomposed below 130° C. (234° F.).) The dark brown residue, after cooling, was examined with the microscope and found to contain the crystalline plates of tyrotoxicon-potassium hydrate, along with the prisms of potassium nitrate. The former was separated from the latter by extraction with absolute alcohol and filtration. The alcohol was evaporated to dryness on the water-bath, and the residue again extracted with absolute alcohol. From this alcoholic solution tyrotoxicon was precipitated with ether. The precipitate was decomposed by adding acetic acid and heating, the tyrotoxicon being broken up into nitrogen and phenol. The phenol was recognized by precipitation with bromine water, and by other well-known tests.

"On October 8th, the coroner's inquest, which had been adjourned after the post-mortem in order to await the results of the analysis, was resumed, and after hearing the testimony in accordance with the above stated facts, the jury returned a verdict of death from poisoning with tyrotoxicon."

Poisonous Ice-cream. — In 1886, Vaughan and Novy obtained tyrotoxicon from a cream which had

seriously affected many persons at Lawton, Michigan. Vanilla had been used for flavoring, and it was supposed that the ill-effects were due to the flavoring. This belief was strengthened by the fact that a portion of the custard was flavored with lemon, and the lemon cream did not affect any one unpleasantly. Fortunately, some of the vanilla extract remained in the bottle from which the flavoring for the ice-cream had been taken, and this was forwarded to the chemists. Each of the experimenters took at first thirty drops of the vanilla extract, and no ill-effects following this, one of them took two teaspoonfuls more, with no results. This proved the non-poisonous nature of the vanilla more satisfactorily than could have been done by a chemical analysis.

Later, it was found that that portion of the custard which had been flavored with lemon was frozen immediately; while that portion which was flavored with vanilla and which proved to be poisonous, was allowed to stand for some hours in a building, which is described as follows by a resident of the village:

"The cream was frozen in the back end of an old wooden building on Main Street. It is surrounded by shade, has no underpinning, and the sills have settled into the ground. There are no eve-troughs, and all the water falling from the roof runs under the building, the streets on two sides having been raised since the construction of the house. The building had been unoccupied for a number of months, consequently had had no ventilation, and what is worse, the back end (where the cream was frozen) was last used as a meat market. The cream which was affected was that portion last frozen; consequently it stood in an atmosphere like that of a privy vault for upward of an hour and a half or two hours before being frozen."

The symptoms observed in these cases are given by Dr. MOFITT as follows:

"About two hours after eating the cream every one was taken with severe vomiting, and after from one to six hours later with purging. The vomit was of a soapy character, and the stools watery and frothy. There was some griping of the stomach and abdomen, with severe occipital headache, excruciating backache, and bone pains all over, especially marked in the extremities. The vomiting lasted from two to three hours, then gradually subsided, and everybody felt stretchy, and yawned in spite of all resistance. The throats of all were œdematous. One or two were stupefied; others were cold and experienced some muscular spasms. A numb feeling, with dizziness and momentary loss of consciousness, was complained of by some. Temperature was normal, and pulse from 90 to 120. Tongue dry and chapped. All were thirsty after the vomiting subsided, and called for cold water, which was allowed in small quantities, with no bad results. After getting out no one of the victims was able to be in the hot sun for several days, and even yet (about ten days after the poisoning) the heat affects myself. I attended twelve persons, besides being sick myself, and all were affected in pretty much the same way. Several complain yet of inability to retain food on the stomach without distressing them. The man who made the cream took a teaspoonful of it, and he vomited the same as those who took a whole dish, but not so often or for so long a time. All are affected with an irresistible desire to sleep, which can scarcely be overcome. Even yet, some of us feel that drowsy condition, with occasional occipital headache."

The tyrotoxicon obtained from this cream was administered to a kitten about two months old. Within ten

minutes the cat began to retch and soon it vomited. This retching and vomiting continued for two hours, during which the animal was under observation, and the next morning it was observed that the animal had passed several watery stools. After this, although the animal could walk about the room, it was unable to retain any food. Several times it was observed to lap a little milk, but on doing so it would immediately begin to retch and vomit. Even cold water produced this effect. This condition continuing, after three days the animal was placed under ether and its abdominal organs examined. Marked inflammation of the stomach was supposed to be indicated by the symptoms, but the examination revealed the stomach and small intestine filled with a frothy, serous fluid, such as had formed a portion of the vomited matter, and the mucous membrane very white and soft. There was not the slightest redness anywhere. The liver and other abdominal organs seemed normal.

A bit of the solid portion of this cream was added to some normal milk, which, by the addition of eggs and sugar, was made into a custard. The custard was allowed to stand for three hours in a warm room, after which it was kept in an ice-box until submitted to chemical analysis. In this tyrotoxicon was also found.

Tyrotoxicon has since been found in some chocolate cream which poisoned persons at Geneva, N. Y., and in lemon cream from Amboy, Ohio.

SCHEARER reports the finding of tyrotoxicon in both vanilla and lemon ice-cream which made many sick at Nugent, Iowa.

ALLABEN reports poisoning with lemon cream, and makes the following interesting statements concerning it:

"I would first say July 4, 5, and 6 were very warm.

Monday evening, July 5, the custards were cooked, made from Monday morning's cream and Monday night's milk, boiled in a tin pan that had the bright tin worn off. It was noticed that one pan of cream was not sweet, but thinking it would make no difference, it was used; the freezers were thoroughly cleaned and scalded, and the custards put in the same evening while hot; the cream was frozen Tuesday afternoon, having stood in the freezers since the night before, when the weather was very warm."

No analysis of this cream was made, but the symptoms agree with those of tyrotoxicon poisoning.

WELFORD observed several cases of poisoning from custard flavored with lemon. These custards were tested for mineral poisons, with negative results.

MORROW has put forth the claim that ice-cream poisoning is solely due to vanilla, which is, according to his statement, used instead of vanilla extract, but the facts stated above concerning poisoning with creams in which other flavors had been used contradict this claim. Moreover, GIBSON has shown the utter absurdity of the claim, inasmuch as he calculates from the amount of flavoring ordinarily used in ice-cream, that in order to produce the toxic symptoms observed, the flavoring must be ten times as poisonous as pure strychnia.

BARTLEY suggests that poisonous cream sometimes results from the use in its manufacture of poor or putrid gelatine. This is highly probable, and with the gelatine the germs of putrefaction may be added to the milk.

POISONOUS MEAL AND BREAD.—Reference has already been made to the fact that the peasants in certain parts of Italy are frequently poisoned by eating mouldy corn-meal. As has also been stated, LOMBROSO and others have ob-

tained from this meal ptomaines, some of which give the same color reaction as strychnine. In 1886, LADD succeeded in isolating from "heated" corn-meal a ptomaine which forms in urea-like crystals. The quantity was not sufficient for an ultimate analysis, and the physiological action has not been studied. Poisoning from decomposed and mouldy bread is not unknown.

CHAPTER III.

THE RELATION OF PTOMAINES TO DISEASE.

That specific microörganisms are concerned in the causation of certain diseases cannot now be questioned. The evidence on this point, for a few diseases at least, amounts to a positive demonstration. The rules given by Koch for determining whether or not a given bacterium is the cause for a certain disease do not admit of any question when they are fully complied with. While it is not our purpose to treat of questions of bacteriology, it may be well in order to discuss intelligently the relation of ptomaines to disease, and in order to have the chain of evidence unbroken, to give briefly these rules. In a condensed form they may be stated as follows:

(1) The special bacterium must be present in all cases of that disease.

The importance of this rule is self-evident. If one case of the disease could be found in which the microörganism did not exist, then its supposed causal relation to that disease must be false. However, the invariable presence of any germ in a certain disease does not prove that the former is the cause of the latter. Indeed, so long as the investigation goes no further than this, we are justified in saying that the microörganism may be an accompaniment or a consequence of the disease. Therefore, additional evidence is wanting and is furnished by complying with the other rules of Koch.

(2) The special microörganism must be freed from other

organisms and from all matter found with it in the diseased animal.

This is done by carrying the organism through successive cultures.

(3) The special germ, thus freed from all foreign matter, must, when properly introduced, produce the disease in healthy animals.

(4) The microörganism must be found properly distributed in the animal in which the disease has been induced.

All of these conditions must be fulfilled before it can be satisfactorily demonstrated that a specific organism is the cause of a given disease, and in certain diseases this complete demonstration has been made.

Recognizing the fact that germs do bear a causal relation to some diseases, the question arises, How do these organisms produce disease? In what way does the bacillus anthracis, for instance, induce the symptoms of the disease and death? Many answers to this question have been offered. Some of the most important of these are as follows:

(1) It was first suggested by BOLLINGER that apoplectiform anthrax was due to deoxidation of the blood by the bacilli. These germs are aërobic, and were supposed to deprive the red blood-corpuscles of their oxygen. This theory was suggested most probably by the resemblance of the symptoms to those of carbonic acid poisoning. The most prominent of these symptoms are dyspnœa, cyanosis, convulsions, dilated pupils, subnormal temperature, and, in general, the phenomena of asphyxia. Moreover, post-mortem examination reveals conditions similar to those observed after death by deprivation of oxygen. The veins are distended, the blood is dark and thick, the parenchymatous organs are cyanotic, and the lungs hyperæmic.

BOLLINGER compared this form of anthrax to poisoning with hydrocyanic acid, which was then believed to produce fatal results by robbing the blood of its oxygen.

This theory was supported by the observations of SZPILMANN, who found that while the putrefactive bacteria were destroyed by ozone, the bacillus anthracis thrived and multiplied in this gas.

This theory presupposed a large number of bacilli in the blood, and this accorded with the estimate of DAVAINE, which placed the number at from eight to ten million in a single drop. But more extended and careful observation showed that the blood of animals dead from anthrax is often very poor in bacilli. VIRCHOW reported cases of this kind. BOLLINGER himself found the bacilli often only in certain positions and not abundant in the blood. Then SIEDAMGROTZKY counted the organisms in the blood in various cases and found not only that the estimate made by DAVAINE was too large, but that in many instances the number present in the blood was small. JOFFROY found in some of his inoculation experiments that the animals died before any bacilli appeared in the blood. These and other investigations of similar character began to cause workers in this field of research to doubt the truth of the theory of BOLLINGER. These doubts were soon converted into positive evidence against the theory. PASTEUR, in support of the theory, reported that birds were not susceptible to anthrax, and he accounted for this by supposing that the blood corpuscles in birds do not part with their oxygen readily. However, it was shown by OEMLER and FESER that the learned Frenchman had generalized from limited data, and that many birds are especially susceptible to the disease. OEMLER found that the blood even when rich in bacilli still possessed the bright red color of oxy-

hæmoglobin. TOEPPER and ROLOFF reported cases of apoplectiform anthrax in which there was no difficulty in respiration. TOUSSAINT caused animals which had been inoculated with the anthrax bacillus to breathe air containing a large volume of oxygen, and found that this did not modify the symptoms or retard death. Finally, NENCKI determined the amount of physiological oxidation going on in the bodies of animals sick with anthrax by estimating the amount of phenol excreted after the administration of one gram of benzol, and found that the oxidation of the benzol was not diminished by the disease. Thus, the theory that germs destroy life by depriving the blood of its oxygen has been found not to be true for anthrax, and if not true for anthrax, certainly it cannot be for any other known disease. The bacillus anthracis is, as has been stated, aërobic, while most of the pathogenic bacteria are anaërobic—that is, they live in the absence of oxygen. This element is not necessary to their existence, and, indeed, when present in large amount, it is fatal to their existence. Moreover, in many diseases, the bacteria are not found in the blood at all. Lastly, the symptoms of these diseases are not those of asphyxia. These facts have caused all bacteriologists to acknowledge that this theory is not the right one.

(2) If a properly stained section of a kidney taken from a guinea-pig, which has been inoculated with the bacillus anthracis, be examined under a microscope, the bacilli will be found to be present in such large numbers that they form emboli, which not only close, but actually distend the capillaries and larger bloodvessels, and interfere with the normal functions of the organ. A similar condition is sometimes found on microscopical examination of the liver, spleen, and lungs. From these appearances, it was inferred

by BOLLINGER that the bacilli produce the diseased condition simply by accumulating in large numbers in these important organs, and mechanically interrupting their functions. This is known as the mechanical interference theory.

KLEBS and TOUSSAINT were formerly ardent advocates of this theory in its application to anthrax, and the latter thought that the symptoms and death are due to stoppage of the pulmonary circulation by means of emboli. However, HOFFA studied this point by making numerous post-mortem examinations, and was unable to confirm it. A like result followed the work of VIRCHOW, COLIN, and SIEDAMGROTZKY, and the mechanical interference theory has been abandoned.

In the majority of germ diseases this theory never had any support. There is not found any great accumulation of bacteria in any organ, and the number and distribution of the germs are such that the theory of mechanical interference cannot be held at all.

(3) Another answer given to the question, How do germs cause disease? is, that they do so by consuming the proteids of the body and thus deprive it of its sustenance. The proteids are known to be necessary for the building up of cells, and it is also known that microörganisms feed upon proteids. But this theory is untenable for several reasons. In the first place, many of the infectious diseases destroy life so quickly that the fatal effect cannot be supposed to be due to the consumption of any very large amount of proteid. In the second place, the distribution of the microörganisms is such in many diseases that they do not come in contact with any large proportion of the proteids of the body. In the third place, the symptoms of the majority of these diseases are not those which would

be produced by withdrawing from the various organs their food. The symptoms are not those of general starvation.

(4) Still another theory, which has been offered, is that the bacteria destroy the blood corpuscles, or lead to their rapid disintegration. But in many of the infectious diseases, as has been stated, the microörganisms, although very abundant in some organs, are not present in the blood at all. Moreover, the disintegration of the blood corpuscles is not confirmed by microscopical examination.

(5) Seeing the vital deficiencies in the above theories, and being impressed by the results obtained by the chemical study of putrefaction, bacteriologists have been led to inquire into the possibility of the symptoms of the infectious diseases being due to chemical poisons. In investigating this theory, three possibilities suggest themselves :

(*a*) The microörganisms themselves may be poisonous, or the poison may be an integral part of them. NEELSEN, at one time an advocate of this theory, thus accounted for the appearance and increase in violence of the symptoms as the germs increase in numbers. In order for the conditions of this theory to be fulfilled, the microörganisms must be present in the blood before any of the symptoms appear. But in anthrax, the most thoroughly studied of all the infectious diseases, and the one to which all these theories have been applied, the bacilli first appear in the blood, as a rule, only a few hours before death, and long after the appearance of the first symptoms; while in many other diseases the germs are never found in the blood. Moreover, as HOFFA has shown, if this theory be true, the injection of a large quantity of anthrax bacilli directly into the blood should be followed immediately by symptoms of the disease, and death should be speedy. But he found, on making experiments of this kind, that the symptoms did

not appear until from twenty-four to seventy-two hours. Finally, NENCKI, by chemical analysis of the substance of anthrax bacilli, has shown that in some respects it resembles vegetable casein, and in others, animal mucin. This "anthrax-protein" is freely soluble in alkalies, is insoluble in water, acetic acid, and the dilute mineral acids. It contains no sulphur, and is not poisonous.

(*b*) The microörganisms may be intimately associated with or may produce a soluble, chemical ferment, which, by its action on the body, produces the symptoms of the disease and death. This theory formerly had a number of ardent supporters, among whom might be mentioned the eminent scientist, DE BARY. But PASTEUR proved the theory false when he filtered anthrax blood through earthen cylinders, inoculated animals with the filtrate, and failed to produce any effect. NENCKI made a similar demonstration when he inoculated a two per cent. gelatine preparation with the anthrax bacillus, which liquefied the preparation, and on standing the bacilli settled to the bottom. The supernatant fluid, which was clear, alkaline in reaction, and contained dissolved "anthrax-protein," was filtered and injected into animals without producing any effect.

(*c*) The bacillus may produce a chemical poison by splitting up preëxisting, complex compounds in the body. This theory is supported by analogy, when we remember that the ordinary putrefactive germs produce such chemical poisons, as has been demonstrated by the work of PANUM and others. These poisons are ptomaines, and the truth of this theory may now be said to amount to a positive demonstration. We now expect to find each specific, pathogenic microörganism producing its own characteristic poison or poisons. The evidence on this point we will give

further on in a brief sketch of some of the best known infectious diseases.

Before taking up the individual diseases, we will give what appears to us, in the present state of our knowledge, a correct definition of an infectious disease.

An infectious disease arises when a specific, pathogenic microörganism, having gained admittance to the body, and having found the conditions favorable, grows and multiplies, and in so doing elaborates a chemical poison which induces its characteristic effects.

In the systemic infectious diseases, such as anthrax, typhoid fever, and cholera, this poison is undoubtedly taken into the general circulation, and affects the central nervous system. In the local infectious diseases, such as gonorrhœa, and infectious ophthalmia, the principal action of the poison seems to be confined to the place of its formation. Though even in these, when of a specially virulent type, the effects may extend to the general health. It may be that in some diseases the chemical poison has both a local and a systemic effect. Thus, it is by no means certain that the ulceration of typhoid fever is due directly to the bacillus. On the other hand, it is altogether probable that the anatomical changes in the intestine result from the irritating effects of the ptomaine at the place of its formation.

In a recent article, NEELSEN has given the following classification of germ diseases:

(1) *General acute mycoses.* In this class of diseases, the germ grows exclusively in the bloodvessels, from which it is not able to escape. However, at the point of inoculation it may produce lesions in the form of inflammatory œdema or hemorrhagic infiltration. As types of this class, may be mentioned anthrax, and mouse-septicæmia.

The deleterious effects do not result from the consump-

tion of any important constituent of the body by the germs, but from the formation of poisons, ptomaines. The injury inflicted by the disease, or the danger to life, will be in proportion to the multiplication of the bacteria, and the consequent amount of the poison produced.

In some of these diseases a very small number of bacteria seem to be able to produce a poison of great intensity. This is true of septicæmia in man and in the rabbit.

To this class belong the intermittent acute mycoses, in which there is only a periodic accumulation of the bacteria in the blood. Recurrent fever is given as an illustration.

(2) *Diseases with local development of bacteria.* In these diseases the bacteria multiply only in the neighborhood of the point of inoculation. These diseases are subdivided into four classes: (*a*) The bacteria developing locally produce a ptomaine, which is absorbed and produces a general intoxication, which is the most prominent symptom of the disease. Cholera, tetanus, and putrid intoxication are examples. (*b*) The general intoxication is present, but is overshadowed by the local inflammatory changes. Malignant œdema, erysipelas, and pneumonia are representatives of this class. (*c*) The local effects lead to necrotic changes, as in hospital gangrene and gangrene foudroyante. (*d*) The local development of the bacteria leads to suppuration.

(3) *Mycoses of the blood with secondary local affections.* The bacteria grow and multiply in the blood, but the most prominent effects of the poison are manifest in local lesions, which may be simply inflammatory, suppurative, or necrotic. As examples of such mycoses with multiple secondary inflammatory lesions, we have, in man, measles, German measles, scarlet fever, acute articular rheumatism, and beriberi ; in the lower animals, chicken cholera.

As mycoses of the blood with secondary suppuration and necrosis, we may mention variola, diphtheria, and osteomalacia.

(4) *Mycoses with tissue proliferation or infective ulcers.* The new formations show a tendency to degenerative changes, suppuration, and necrosis. Such are typhoid fever, glanders, tuberculosis, leprosy, and syphilis.

ANTHRAX.—The definition of an infectious disease, as we have given it, is well illustrated by the facts which have been learned concerning the causation of anthrax, which, probably, has been more thoroughly studied than any other infectious disease. KAUSCH taught that anthrax had its origin in paralysis of the nerves of respiration. DELAFOND thought that the cause of the disease was to be found in the influence of the chemical composition of the soil affecting the food of animals, and leading to abnormal nutrition. The investigations of GERLACH, in 1845, demonstrated the contagious nature of the disease, which was emphasized by HEUSINGER in 1850, and accepted by VIRCHOW in 1855. However, in 1849, POLLENDER found numerous, rod-like microörganisms in the blood of animals with the disease. This observation was confirmed by BRAUELL, who produced the disease in healthy animals, by inoculation with matter taken from a pustule on a sick horse. Attempts were made to ridicule the idea that these germs might be the cause of the disease, and it was said that the bodies seen were only fine pieces of fibrin, or blood-crystals. But, in 1863, DAVAINE showed that these little bodies must have some causal relation to the disease, inasmuch as his experiments proved that inoculation of healthy animals with the blood of animals sick with anthrax produced the disease only when the blood contained these organisms. He

also demonstrated beyond any question, that these bodies were bacteria. The conclusions of this investigator were earnestly combated by many. But PASTEUR, KOCH, BOLLINGER, DE BARY, and others, studied the morphology and life-history of these organisms, and then came the brilliant results of PASTEUR and KOCH in securing protection against the disease by the vaccination of healthy animals with the modified germ. Now, the bacillus anthracis is known in every bacteriological laboratory, and by inoculation with it the disease is communicated at will to animals. But, here the question arose, How do these bacilli produce anthrax? and, in answer to this question, the various theories which we have mentioned were proposed. Recently, HOFFA has given us the true answer by obtaining from pure cultures of the bacillus anthracis a ptomaine which, when injected under the skin of animals, produces the symptoms of the disease followed by death. The anthrax ptomaine causes at first increased respiration and action of the heart, then the respirations become deep, slow, and irregular. The temperature falls below the normal. The pupils are dilated, and a bloody diarrhœa sets in. On section, the heart is found contracted, the blood dark, and ecchymoses are observed on the pericardium and peritoneum.

CHOLERA.—Although the ptomaine of cholera has not been isolated, there are reasons for believing that the comma bacillus of KOCH is one of the most active chemically of all known pathogenic microörganisms. In the first place, BITTER has shown that this germ produces in meat-peptone cultures a peptonizing ferment, which remains active after the organism has been destroyed. It was shown that this ferment, like similar chemical ferments, would convert an

indefinite amount of gelatine or coagulated albumen into peptone. It was also demonstrated that this ferment was more active in alkaline than in acid solutions, thus proving that it resembles pancreatin more than pepsin. This resemblance to pancreatin was further demonstrated by the fact that certain chemicals, such as sodium carbonate and sodium salicylate, increased its activity.

That a diastasic ferment is also produced by the growth of this bacillus was indicated by the development of an acid in nutrient solutions containing starch paste. However, all attempts to isolate the diastasic ferment were unsuccessful. A temperature of 60° destroys or greatly decreases the activity of ptyalin, and this seems to be also true of the diastasic ferment produced by the comma bacillus. But the formation of an acid from the starch presupposes that the starch is first converted into a soluble form.

[It is proper to mention here that STERNBERG, independently of the experiments of BITTER, has shown that a number of microörganisms are capable of producing a peptonizing ferment, which remains active after destroying the germs by raising the temperature of the culture to 80°. STERNBERG experimented with bacillus prodigiosus, b. indicus, b. pyocyanus and FINKLER-PRIOR'S spirillum. It is probable that all germs which liquefy gelatine do so by the production of this ferment.]

In order to investigate the digestive action of bacteria, RIETSCH precipitated peptone cultures of the cholera bacillus, typhoid bacillus, bacillus of consumption, and staphylococcus aureus with alcohol, collected, washed, dried, and weighed the precipitates and tested their action upon coagulated fibrin. The powders thus obtained from cultures of the typhoid and consumption bacilli had no digestive action in either neutral or alkaline fluids. On the other hand, the

precipitates obtained from the cultures of the cholera bacillus and the staphylococcus aureus, the latter less energetically than the former, dissolved the fibrin and the solutions gave reactions for peptones.

RIETSCH believes that the destructive changes observed in the intestines in cholera are due to the action of this peptonizing ferment.

CANTANI injected sterilized cultures of the comma bacillus into the peritoneal cavities of small dogs and observed after from one-quarter to one-half hour the following symptoms: great weakness, tremor of the muscles, drooping of the head, prostration, convulsive contractions of the posterior extremities, repeated vomiting, and cold head and extremities. After two hours these symptoms began to abate, and after twenty-four hours the recovery seemed complete. Control experiments with the same amounts of uninfected beef-tea were made with negative results. These cultures were three days old when sterilized. Older cultures seemed less poisonous, and a high or prolonged heat in sterilization decreased the toxicity of the fluid. From these facts CANTANI concludes that the poisonous principle is volatile. The cultures in bouillon containing peptone were more poisonous than those in simple bouillon.

KLEBS has attempted to answer experimentally the question, In what way does the cholera germ prove harmful? Cultures of the bacillus in fish preparations were acidified, filtered, the filtrate evaporated on the water-bath, the residue taken up with alcohol and precipitated with platinum chloride. The platinum was removed with hydrogen sulphide, and the crystalline residue obtained on evaporation was dissolved in water and injected intravenously into rabbits. Muscular contractions were induced. Death followed in one animal, which, in addition to the above treatment, re-

ceived an injection of a non-sterilized culture. In this case there was observed an extensive calcification of the epithelium of the uriniferous tubules. KLEBS believes this change in the kidney to be induced by the chemical poison, and from this standpoint he explains the symptoms of cholera as follows: The cyanosis is a consequence of arterial contraction, the first effect of the poison. The muscular contractions also result from the action of the poison. The serous exudate into the intestines follows upon epithelial necrosis. Anuria and the subsequent severe symptoms appear when the formation and absorption of the poison become greatest.

HUEPPE states that the severe symptoms of cholera can be explained only on the supposition that the bacilli produce a chemical poison, and that this poison resembles muscarine in its action.

BUJWID found that on the addition of from five to ten per cent. of hydrochloric acid to bouillon cultures of the cholera bacillus, there was developed after a few minutes a rose-violet coloration which increased during the next half hour and in a bright light showed a brownish shade. The coloration is more marked if the culture is kept at about 37°. In impure cultures this reaction does not occur. The FINKLER-PRIOR bacillus cultures give after a longer time a similar, but more of a brownish coloration. Cultures of many other bacilli were tried and failed to give this reaction.

BRIEGER found that this color is due to an indol derivative. In cholera cultures on albumens he obtained indol by distillation with acetic acid.

BUJWID has recently made a further contribution to our knowledge of the "cholera-reaction." His conclusions are as follows:

(1) Five to ten per cent. of hydrochloric acid added to

cholera cultures produce a rose-violet coloration, which is characteristic of the comma bacillus.

(2) No other bacterium gives the same coloration under the same conditions.

(3) The coloration appears in such cultures which are from ten to twelve hours old, so that this test can be used for diagnostic purposes, and will give results before they can be obtained by plate cultures.

(4) Impure cultures do not give this reaction.

DUNHAM finds the best medium for the "cholera-reaction" to be a one per cent. alkaline peptone solution with one-half per cent. of common salt. BUJWID prefers a two per cent. feebly alkaline peptone solution with salt. JADASSOHN finds that gelatine cultures give the reaction both before and after the liquefaction of the gelatine. The undissolved gelatine, after the addition of hydrochloric or sulphuric acid, becomes rose-violet.

COHEN claims that cultures of other bacilli give a similar coloration, but BUJWID explains that the results obtained by COHEN were due to the use of impure acids, which contained nitrous acid. SALKOWSKI agrees with BUJWID, and states that, when acids wholly free from nitrous acid are used, the reaction is characteristic of the comma bacillus. He explains the reaction by supposing that the germ produces nitrous acid, which exists in the culture as a nitrite. On the addition of an acid the nitrous acid is set free, and acting upon the indol, which is also present, gives the coloration.

The reaction can also be obtained by adding crystallized oxalic acid to the culture.

SCHUCHARDT calls attention to the fact that VIRCHOW observed a red coloration on the addition of nitric acid to filtered cholera stools forty years ago. GRIESINGER, in

1885, also made mention of the production of a red coloration in rice-water stools on the addition of nitric acid.

A "cholera-blue" has also been observed by BRIEGER, in cultures in meat extract containing peptone and gelatine. This substance, which is yellow by reflected, and blue by transmitted light, is developed by the addition of concentrated sulphuric acid to the culture. It may be separated from the "cholera-red" as follows: Treat the culture with sulphuric acid, then render alkaline with sodium hydrate, and extract with ether. Evaporate the ether, and remove the "cholera-red" with benzol, then again dissolve the "cholera-blue" in ether. The characteristic absorption bands for this coloring matter begin in the first third of the spectrum, between E and F, and darken all of the zone lying beyond.

VILLIERS isolated by the STAS-OTTO method from two bodies dead from cholera, a poisonous base which was liquid, pungent to the taste, and possessed the odor of hawthorn. It was strongly alkaline, and gave precipitates with the general alkaloidal reagents. From one to two milligrams of this substance, injected into frogs, caused decreased activity of the heart, violent trembling, and death. The heart was found in diastole, and full of blood, and the brain slightly congested. However, the presence of this substance in the bodies of persons who have died of cholera does not prove that its production is due to the cholera bacillus.

POUCHET extracted from cholera stools, with chloroform, an oily base belonging to the pyridine series. It readily reduces ferric as well as gold and platinum salts, and forms an easily decomposable hydrochloride. It is a violent poison, irritating the stomach, and retarding the action of

the heart. Subsequently, he obtained an apparently identical substance from cultures of KOCH's comma bacillus.

BRIEGER has recently made a report upon the ptomaines of cholera. He used pure cultures on beef-broth (fleisch-brei), which was rendered alkaline by the addition of a three per cent. soda solution. These were kept at from 37° to 38°. After twenty-four hours, cadaverine was found to be present. Older cultures furnished very small quantities of putrescine. The lecithin was slowly acted upon by the germs, but with age the amount of choline increased, reaching its maximum during the fourth week.

Creatine proved still more resistant to the action of the germs; but, after six weeks, a considerable quantity of creatinine was isolated, and a smaller amount of methyl-guanidine. The latter is very poisonous, causing muscular tremors and dyspnœa. The presence of methyl-guanidine indicates that the comma bacillus acts as an oxidizing agent, since creatine yields methyl-guanidine only by oxidation.

BRIEGER succeeded in finding, in addition to the above-mentioned ptomaines, which are common products of putrefaction, two poisons which he considers as specific products of the comma bacillus. One of these, found in the mercuric chloride precipitate, is a diamine, resembling trimethylenediamine. It produced muscular tremor and heavy cramps. In the mercury filtrate was found another poison, which, in mice, produced a lethargic condition; the respiration and heart's action became slow, and the temperature sank, so that the animal felt cold. Sometimes there was bloody diarrhœa.

TETANUS.—In 1884, NICOLAIER, by inoculating 140 animals with earth taken from different places, produced symptoms of tetanus in 69 of them. In the pus which

formed at the point of inoculation, he found micrococci and bacilli. Among the latter was one which was somewhat longer and slightly thicker than the bacillus of mouse-septicæmia. In the subcutaneous cellular tissue he found this bacillus alone, but could not detect it in the blood, muscles, or nerves. Heating the soil for an hour rendered the inoculations with it harmless. In cultures, NICOLAIER was unable to separate this bacillus from other germs, but inoculations with mixed cultures produced tetanus. In the same year, CARLE and RATIONE induced tetanus in lower animals by inoculations with matter taken from a pustule on a man just dead from tetanus. In 1886, ROSENBACH made successful inoculations on animals with matter taken from a man who had died from tetanus consequent upon gangrene from frozen feet. With bits of skin taken from near the line of demarcation, he inoculated two guinea-pigs on the thigh; tetanic symptoms set in within twelve hours, and one animal died within eighteen, and the other within twenty-four hours. The symptoms corresponded exactly with those observed in the "earth tetanus" of NICOLAIER, and the same bacillus was found. With mixed cultures of this, ROSENBACH was also able to cause death by tetanus in animals. BEUMER had under observation a man who died from lock-jaw following the sticking of a splinter of wood under his finger-nail. Inoculations of mice and rabbits with some of the dirt found on the wood led to tetanus. The same observer saw a boy die from this disease following an injury to the foot from a sharp piece of stone. White mice inoculated with matter from the wound, and those inoculated with dirt taken from the boy's playground, died of tetanus. The bacillus of NICOLAIER was again detected. GIORDANO reports the case of a man who fell and sustained a complicated fracture of the arm. He

remained on the ground for some hours, and when assistance came the muscles and skin were found torn and the wounds filled with dirt. On the fifth day he showed symptoms of tetanus, from which he died on the eighth day. Inoculations and examinations for the bacillus were again successful. TERRARI also made successful inoculations with the blood taken during life from a woman with tetanus after an ovariotomy. HOCKSINGER has confirmed the above-mentioned observations by carefully conducted experiments, the material for which was furnished by a case of tetanus arising from a very slight injury to the hand, the wound being filled with dirt. SHAKESPEARE has succeeded in inducing tetanus in rabbits by inoculating them with matter taken from the medulla of a horse and of a mule, both of which had died from traumatic tetanus. These uniform observations leave no room to doubt that tetanus is often, at least, due to a germ which exists in many places in the soil, and that the disease is transmissible by inoculation.

BONOME observed nine cases of tetanus among seventy persons injured by the falling of a church from the earthquake at Bajardo. The bacillus of NICOLAIER was detected in the wounds, and animals inoculated with the lime-dust of the fallen building died of tetanus. Of many persons injured by the falling of another church at the same time, none had tetanus, and animals inoculated with the lime from this church suffered no inconvenience.

The same experimenter found the bacillus in the wound of a sheep which died from tetanus after castration.

BEUMER found the tetanus bacillus in the sloughing tissue of the umbilical cord of a child which was taken ill on the sixth day after birth, and died four days later from tetanus. From this he concludes that tetanus neonatorum

and "earth tetanus" are identical, and advises that the cord should be dressed antiseptically.

The question now arises, How do these germs induce tetanus? BRIEGER has given us an answer inasmuch as he has obtained in cultures of the germ of NICOLAIER and ROSENBACH four poisonous substances. The first, tetanine, which rapidly decomposes in acid solutions, but is stable in alkaline solutions, produces tetanus in mice when injected in quantities of only a few milligrams. The second, tetanotoxine, produces first tremor, then paralysis followed by severe convulsions. The third, to which no name has been given, causes tetanus accompanied by free flow of the saliva and tears. The fourth, spasmotoxine, induces heavy clonic and tonic convulsions.

It may be that all these will be found to be modifications or impure forms of the same poison. BRIEGER states that the exact character and relative amounts of the poisons formed vary with the nutrient in which the germ grows.

With this evidence before us, we feel justified in saying that the tetanus germ produces its poisonous effects by elaborating one or more ptomaines in the body of the animal into which it has been introduced.

TYPHOID FEVER. — This disease also illustrates the definition which we have given of an infectious disease. In 1880, EBERTH discovered a bacillus which he believed to be the cause of typhoid fever, and this belief has been confirmed. The fever, with its characteristic lesions, has been produced in animals by inoculation with the germ. GAFFKY was the first to inoculate animals with pure cultures of the bacillus of EBERTH, but his results were wholly negative. FRÄNKEL and SIMMONDS produced fatal

results and observed after death enlargement of the spleen, mesenteric glands, and intestinal follicles. Moreover, microscopical examination of the spleen showed the same conditions which are found in the spleen of persons dead of typhoid fever. SEITZ, using KOCH'S method of cholera inoculation, produced with the typhoid bacillus acute enteritis, with ulceration and enlargement of the spleen. VAUGHAN and NOVY, using the germ which they had obtained from drinking water, produced in a cat vomiting, great muscular weakness or prostration, primary depression of temperature four degrees below the normal, and secondary elevation of temperature three degrees above the normal. Section showed ulceration in both the small intestine and ascending colon. Results of this kind leave no doubt that the bacillus first described by EBERTH is the true germ of typhoid fever.

In 1885, BRIEGER obtained from pure cultures of the typhoid bacillus a toxic ptomaine, which produced in guinea-pigs a slight flow of saliva, frequency of respiration, dilatation of the pupils, profuse diarrhœa, paralysis, and death within from twenty-four to forty-eight hours. Post-mortem examination showed the heart in systole, the lungs hyperæmic, and the intestines contracted and pale. This substance BRIEGER considers the special poison of typhoid fever, and calls it typhotoxine. However, he obtained with this poison no elevation of temperature.

In 1887, VAUGHAN and NOVY obtained from pure cultures of the typhoid bacillus, found in drinking water which had been the supply for many persons who had the disease, an extract which, when injected under the skin of cats, caused an elevation in the temperature of from two to four and one-half degrees above the normal.

SIROTININ and BEUMER and PEIPER have produced the

same pathological phenomena by inoculating animals with sterilized cultures that they obtained with the germ. They found that the severity of the symptoms varied with the amount of the culture injected.

In one sick of typhoid fever, the bacillus grows and multiplies in the intestines and forms the poison, the absorption of which is followed by the rise in temperature and other symptoms of the disease. The lesions in the intestines are probably due to the bacteria themselves, or possibly to the local irritating effect of the ptomaine.

Cholera Infantum.—There are many reasons for believing that this disease is sometimes at least due to poisoning by tyrotoxicon. The fact that infants nourished exclusively from the mother's breast are almost wholly exempt from the disease strengthens this belief. We have already seen how quickly and abundantly this poison appears in milk when the conditions are favorable. Moreover, the symptoms induced by the poison agree with those observed in the disease, and the post-mortem changes are identical. Cholera infantum is a disease of the summer months, when decomposition in milk goes on most readily. It is most common in cities and among classes who cannot obtain fresh milk or have not the means necessary to keep it fresh. Moreover, it is often allowed to stand in a foul atmosphere, and all know that milk readily takes up disagreeable odors. Even in the country, insufficient attention is given to the care of milk. Cows stand and are milked in filthy barns. The udders are generally not washed before the milking, and the vessels for the milk are frequently not as clean as they should be. There can be no doubt that greater attention to the milk used by

infants would result in saving many thousands of lives annually.

PUERPERAL FEVER.—BOURGET claims to have isolated several ptomaines from the urine of women with puerperal fever. His conclusions are as follows: (1) In puerperal fever the urine contains highly poisonous bases. (2) The toxicity of the urine is most marked when the symptoms of the disease are most grave, and diminishes as the symptoms abate. (3) The ptomaines obtained from the urine prove fatal when injected into frogs and guinea-pigs. (4) Toxic bases, resembling those obtained from the urine, were extracted from the viscera of a woman who had died of puerperal fever.

IMMUNITY FROM DISEASE SECURED BY INTOXICATION WITH PTOMAINES.—SALMON and SMITH ascertained that pigeons may be protected from the fatal effects which ordinarily follow inoculation with cultures of the hog cholera bacillus by first injecting into their tissues two doses of one cubic centimeter each of a culture liquid in which the microbe had been allowed to multiply and had afterward been destroyed by heat. In other words, they found that injection of the ptomaine conferred immunity from the effects of the living germ. However, they have been unable, up to the present time, to secure immunity from the disease in hogs by this method.

CHANTEMESSE and VIDAL, and others, have found that severe intoxication of animals with sterilized cultures of the typhoid bacillus protects against subsequent inoculation with the germs. This has led to the supposition that man might be protected from this disease by the same method.

ROUX and CHAMBERLAND have recently shown that

injections of sterilized cultures of the germ of septicæmia (*malignant œdema* of KOCH and GAFFKY, *gangrène gazeuse* of CHAUVEAU and ARLOING) give immunity from the effects of the living germ, as is proven by subsequent inoculation.

PASTEUR is inclined to the belief that the protection which he secures against hydrophobia is due to the action of a chemical substance, or a ptomaine, and not to a living germ. PASTEUR and PERDRIX have made some experiments which go to show that the injection of sterilized anthrax blood affords protection against subsequent inoculation with the bacillus anthracis in rabbits.

These experiments are of the greatest value. However, it is too early yet to assert that the immunity thus secured by intoxication with ptomaines is identical with that secured against smallpox by vaccination. Grant that PASTEUR is right in supposing that his method of securing immunity against hydrophobia is due to a chemical substance and not to a living organism (and we think his method is most rationally explained in this way), then the question arises, Has he really vaccinated the person against hydrophobia, or has he simply established a tolerance for the poison of hydrophobia? The period of continuance of the immunity should be determined. SEWALL found that he could establish a tolerance for the venom of the rattlesnake in pigeons, but after six months the tolerance was lost.

CHAPTER IV.

THE IMPORTANCE OF PTOMAINES TO THE TOXICOLOGIST.

The presence in the cadaver of substances, which give not only the general alkaloidal reactions but respond to some of the tests which have hitherto been considered characteristic of individual vegetable alkaloids, must be of the greatest importance to toxicologists. The possibility of mistaking putrefactive for vegetable alkaloids should always be borne in mind by the chemist in making his medico-legal investigations. On the other hand, as we have seen in preceding chapters, cases of poisoning by ptomaines sometimes terminate fatally, and in such instances the chemist should not be satisfied with determining the absence of mineral and vegetable poisons, but should strive to detect in the food or in the dead body positive evidence of the presence of the putrefactive alkaloid.

In this chapter we will give an account of those cases in which putrefactive substances have been found to resemble in their reactions the vegetable alkaloids.

Coniine-like Substances.—The most celebrated case in which a substance giving reactions similar to those of coniine has been found, was the Brandes-Krebs trial, which took place in Braunschweig in 1874. From the undecomposed parts of the body two chemists obtained, in addition to arsenic, an alkaloid which they pronounced coniine. This substance was referred to Otto for further examination. Otto reported that the substance was neither coniine nor

nicotine, nor any vegetable alkaloid with which he was acquainted. OTTO converted the substance into an oxalate, dissolved it in alcohol, evaporated the alcohol, dissolved the residue in water, rendered this solution alkaline with potash, then extracted the base with petroleum ether. On evaporation of the petroleum ether the alkaloid appeared as a bright yellow oil, which had a strong, unpleasant odor, quite different, however, from that of coniine. It was strongly alkaline and had an intensely bitter taste. At ordinary temperature, it was volatile. From its aqueous solution it was precipitated by the chlorides of gold, platinum, and mercury. In these reactions it resembled nicotine, from which it differed in the double refractive and crystalline character of its hydrochloride. With an ethereal solution of iodine this substance did not give the ROUSSIN test for nicotine, but instead of the long ruby-red crystals, there appeared small, dark green, needle-shaped crystals.

This substance was found to be highly poisonous. Seven centigrams injected subcutaneously into a large frog produced instantaneous death, and forty-four milligrams given to a pigeon caused a similar result. On account of its poisonous properties the jury of medical experts decided that the substance was a vegetable alkaloid. OTTO says that this decision astounded the chemists.

BROUARDEL and BOUTMY found in the body of a woman who had died, after suffering with ten other persons, from choleraic symptoms from eating of a stuffed goose, a base which gave the odor of coniine and the same reactions with gold chloride and iodine in potassium iodide, etc., as coniine. The same base was found in the remainder of the goose. But it did not give a red coloration with the vapor of hydrochloric acid, and it did not form butyric acid on

oxidation, and although it was poisonous, it did not produce in frogs the symptoms of coniine poisoning.

SELMI repeatedly found coniine-like substances in decomposing animal tissue. By distilling an alcoholic extract from a cadaver, acidifying the distillate with hydrochloric acid, evaporating, treating the residue with barium hydrate and ether, and allowing the ether to evaporate spontaneously, he obtained a residue of volatile bases, the greater part of which consisted of trimethylamine. After removing the trimethylamine, the residue had the odor of the urine of the mouse. Later, SELMI obtained an unmistakable coniine odor from a chloroform extract of the viscera of a person who had been buried six months, and in another case ten months after burial. Two or three drops of an aqueous solution of the alkaline residue of the chloroform extract allowed to evaporate on a glass plate gave off such a penetrating odor that SELMI was compelled to withdraw from close proximity with the substance. The odor imparted to his hands in testing the substance with the general alkaloidal reagents remained for half an hour. This volatile base seemed to be formed by the spontaneous decomposition of other ptomaines.

An aqueous solution of a ptomaine obtained by SELMI by extraction with ether according to the STAS-OTTO method from the undecomposed parts of a cadaver had no marked odor, but after having been kept for a long time in a sealed tube it not only gave off a marked coniine odor, but the vapor turned red litmus paper blue. Again, the sulphate of a ptomaine obtained from putrid egg-albumen formed on standing in two layers, one of which was a golden-yellow liquid, which, on being treated with barium hydrate, gave off ammonia, and later, the odor of coniine. Since butyric and acetic acids were formed by the oxidation of this base,

SELMI concluded that he had real coniine or methylconiine, and that it was formed by the oxidation of certain fixed ptomaines, or by the action of different amido-bases on volatile fatty acids. Therefore, SELMI believed in the spontaneous origin of coniine or closely allied bases in putrid matter, also in the existence of a "cadaveric coniine."

The substance which was found by SONNENSCHEIN in a criminal trial in East Prussia, and which was believed by that chemist to be the alkaloid of the water hemlock (cicuta virosa), is thought by OTTO, HUSEMANN, and others, to be a cadaveric coniine. OTTO says that the symptoms reported in the case were not those of either coniine or cicuta. SONNENSCHEIN obtained the base six weeks after the exhuming of the body, which had been buried three months. The base had the odor of coniine, the taste of tobacco, gave with potassium bichromate and sulphuric acid the odor of butyric acid, and behaved with reagents like coniine.

HUSEMANN states that at present it is very difficult, if not impossible, for the chemist to state with certainty that he has detected true coniine in the dead body. The symptoms and the post-mortem appearances must conform with those induced by the vegetable alkaloid. The analysis must be made before decomposition sets in, and the amount of the base found must be sufficient for physiological experiments to be made with it.

A NICOTINE-LIKE SUBSTANCE.—WOLCKENHAAR obtained from the decomposed intestines of a woman who had been dead six weeks, by extraction with ether from an alkaline solution, a base which bore a close resemblance to nicotine. The base was fluid, at first yellow, but on being exposed to the air, brownish-yellow. It was strongly alkaline in reaction and gave off an odor resembling nicotine,

but stronger, not ethereal, but benumbing and similar to that of fresh poppy-heads. It was soluble in all proportions in water, and the solutions, which did not become cloudy on the application of heat, did not taste bitter, but were slightly pungent. The peculiar odor did not disappear on saturating the base with oxalic acid. The hydrochloride was yellow, like varnish, had a strong odor, and became moist on exposure to the air. Under the microscope it showed no crystals, differing in this respect from nicotine hydrochloride. It differed from nicotine also in its reactions with potassio-bismuthic iodide, gold chloride, iodine solution, mercuric chloride, and platinum chloride. It also failed to give the ROUSSIN test for nicotine. Moreover, it could not be identified with trimethylamine, sparteine, mercurialine, lobeline, or other fluid and volatile bases.

The studies of RÖRSCH and FASSBENDER (page 25), of SCHWANERT (page 26), of LIEBERMANN (page 27), and of SELMI (page 28), have already been referred to in a preceding chapter.

STRYCHNINE-LIKE SUBSTANCES.—In a criminal prosecution at Verona, CIOTTA obtained from the exhumed, but only slightly decomposed body, an alkaloid which gave a crystalline precipitate with iodine in hydriodic acid, a red coloration with hydriodic acid, and a color test similar to that of strychnine with sulphuric acid and potassium bichromate, and with other oxidizing agents. This substance was strongly poisonous, but did not produce the tetanic convulsions which are characteristic of strychnine. CIOTTA pronounced this substance as probably identical with strychnine. Portions of the body were subsequently submitted to SELMI for his opinion. SELMI found that the substance which gave the color reaction was not crystalline,

and that there was only "the presumption of a bitter taste to it," while one part of strychnine in 40,000 parts of water is intensely bitter. SELMI also held that many ptomaines give reactions similar to strychnine with iodine in hydriodic acid, and with hydriodic acid. He also held that its physiological properties were such that it could not be strychnine. This substance could hardly have been aspidospermine, which reacts with sulphuric acid and potassium bichromate similar to strychnine, because quebracho bark, in which this alkaloid is found, was not at that time used as a medicine or known in Italy.

Ptomaines giving reactions similar to those of strychnine, and also causing tetanic spasms, have been found in Italy in decomposed corn-meal. SELMI obtained one of these substances, but found that it differed from strychnine inasmuch as it could not be extracted with ether.

LOMBROSO has named the poisonous substance found in decomposed corn-meal pellagroceine, but this is really a mixture of ptomaines, some of which produce narcosis and paralysis, and others produce the symptoms of nicotine poisoning instead of the spasms caused by strychnine.

A MORPHINE-LIKE SUBSTANCE.—In the Sonzogna trial, at Cremona, Italy, the experts seem to have confounded a ptomaine with morphine. This substance was not removed from either alkaline or acid solutions with ether, but could be extracted with amylic alcohol. It reduces iodic acid, but in its other reactions, as well as in its physiological properties, it bore no resemblance to morphine. In frogs it arrested the heart in systole, which is said never to happen in poisoning with morphine. It failed to give both the ferric chloride and the Pellagri tests for morphine.

In the same body there was found a substance which was

extracted from alkaline solutions with ether, and which gave, with hydrochloric acid and a few drops of sulphuric acid, on the application of heat, a reddish residue similar to that obtained by the same reagents with codeine, but in its other reactions it did not resemble this alkaloid.

ATROPINE-LIKE SUBSTANCES.—Many investigators have found products of putrefaction which in their mydriatic properties resemble atropine and hyoscyamine. To this class belongs the substance observed by ZUELZER and SONNENSCHEIN. It was removed from alkaline solutions by ether, and formed microscopic crystals, an aqueous solution of which, when applied to the conjunctiva, produced a mydriatic effect, and, when administered internally, increased the action of the heart and arrested the movements of the intestines. Moreover, with certain alkaloidal reagents, such as platinum chloride, it resembled atropine. But when heated with sulphuric acid and oxidizing agents it did not give the odor of blossoms (REUSS'S test). However, SELMI found ptomatropines which with sulphuric acid and oxidizing agents did give the blossom odor as distinctly as the vegetable atropine. These putrefactive bases also developed this odor spontaneously after standing for two or three days, and this does not happen with atropine. The odor was produced with the ptomatropines by nitric and sulphuric acids, both in the cold and on the application of heat, while these acids in the cold do not produce the odor with atropine.

DIGITALINE-LIKE SUBSTANCES.—Elsewhere we have referred to the discovery of a ptomaine belonging to this class by RÖRSCH and FASSBENDER (see page 26). TROTTARELLI obtained a similar substance from the brain of a

man in whose abdominal viscera he could find no poison. The sulphate of this base gave on evaporation an aromatic-smelling and astringent-tasting residue. It became purple with sulphuric acid alone, and dark red with hydrochloric and sulphuric acids. On frogs this ptomaine showed no toxic effect.

A Veratrine-like Substance.—Brouardel and Boutmy obtained from a corpse which had lain in water for eighteen months, and a large portion of which had changed into adipocere, a ptomaine resembling veratrine. It was removed from alkaline solutions by ether. On being heated with sulphuric acid it became violet. With a mixture of sulphuric acid and barium peroxide it became, in the cold, brick-red; and, on being heated, violet. With boiling hydrochloric acid it took on a cherry-red coloration. However, it differed from veratrine, inasmuch as it reduced ferric salts instantly, and when injected into frogs subcutaneously it did not induce in them the spasmodic muscular contractions characteristic of veratrine.

Bechamp obtained by the Stas-Otto method from the products of the pancreatic digestion of fibrin an alkaloid body which gave with sulphuric acid a beautiful carmine-red, similar to that given with veratrine. By digesting this substance with gastric juice, and again extracting, he obtained a body which behaved with sulphuric acid similar to curarine.

A Delphinine-like Substance.—In 1870, General Gibbone, an Italian of prominence, died suddenly. His servant was accused of having poisoned him. Two chemists of some reputation reported the presence of delphinine in the viscera. It seemed somewhat improbable that the

servant should know anything of so rare a substance, or that he should have been able to obtain it. However, two or more varieties of staphisagria grow in Southern Italy, and it was possible that the servant had used some preparation made by himself from the plant. The supposed alkaloid was given to SELMI, of Bologna, for further study. It was removed from alkaline solutions by ether. When heated with phosphoric acid it became red, and when brought in contact with concentrated sulphuric acid, reddish-brown. In these tests the substance resembled delphinine, but with sulphuric acid and bromine water, also with FRÖHDE'S reagent, the colorations characteristic of the vegetable alkaloid failed to appear. Moreover, SELMI showed that delphinine gave the following reactions, to which the suspected substance did not respond : (1) Delphinine dissolved in ether, and treated with a freshly prepared ethereal solution of platinic chloride, gives a white, flocculent precipitate which is insoluble in an equal volume of absolute alcohol. (2) Delphinine gives precipitates with auro-sodium hyposulphite, and with a sulphuric acid solution of cupro-sodium hyposulphite, the latter precipitate being soluble in an excess of the reagent.

Finally, CIACCIA and VELLA showed that while delphinine arrests the heart of the frog in diastole, the suspected substance arrests it in systole.

A COLCHICINE-LIKE SUBSTANCE.—BAUMERT found in a suspected case of poisoning, twenty-two months after death, a substance which gave many of the reactions for colchicine. It was extracted from acid solutions with ether, to which it imparted a yellow color. On evaporation of the ether a yellow, amorphous substance remained, and this dissolved in warm water with yellow coloration. It

could be extracted from acid solutions also by chloroform, benzol, and amylic alcohol, but not by petroleum ether. It was removed with much more difficulty from alkaline solutions.

All the extracts were yellow, and left on evaporation a feebly alkaline, markedly bitter, sharp tasting, amorphous, yellow residue, which dissolved in water and dilute acids incompletely, forming a resin. When this resin was dissolved in dilute sodium hydrate, and the solution rendered acid by sulphuric acid, the same reactions were obtained as with the original extract.

With phosphomolybdic acid, phosphotungstic acid, potassio-bismuthic iodide, potassio-mercuric iodide, iodine in potassium iodide, tannic acid and gold chloride, this substance gave the same reactions which were obtained by parallel experiments with genuine colchicine; thus, the tannic acid precipitates were both soluble in alcohol, and the precipitates with phosphomolybdic acid in both cases became blue on the addition of ammonium hydrate.

Concentrated sulphuric and dilute nitric and hydrochloric acids dissolved the supposed colchicine with yellow coloration. Strong nitric acid (1.4 sp. gr.) colored the substance dirty red, scarcely to be called a violet. When the substance was purified as much as possible, this color became a beautiful carmine-red. The addition of water changed the red into yellow, and caustic soda produced a dark, dirty orange.

In general, in the above-mentioned reactions, the putrefactive product agreed with the real colchicine, but the former gave precipitates with picric acid and platinum chloride, while the latter gives no precipitates with these reagents.

In 1886, Zeisel proposed the following test for colchi-

cine: When a hydrochloric acid solution of the alkaloid is boiled with ferric chloride, it becomes green, sometimes dark green and cloudy. Now, if the fluid be agitated with chloroform, the chloroform will sink, taking up the coloring matter, and appearing brownish, granite-red or dark, and the supernatant fluid clears up without becoming wholly colorless.

BAUMERT applied this test to both colchicine and the putrefactive product. To from two to five cubic centimetres of the suspected solution in a test-tube, he added from five to ten drops of strong hydrochloric acid, and from four to six drops of a ten per cent. solution of ferric chloride, then heated the mixture directly over a small flame until it was evaporated to half its volume or less. In the presence of one milligram of colchicine the originally bright yellow solution became gradually olive-green, and, on further concentration, dark green and cloudy. Then, on shaking the fluid with chloroform, admitting as much air as possible, the chloroform subsided, having a ruby-red color if as much as two milligrams of colchicine were present, and a bright yellow if only one milligram, and the supernatant fluid became of a beautiful olive-green. When ether, petroleum ether, benzol, carbon disulphide, or amylic alcohol was substituted for the chloroform, the coloration did not appear. From this BAUMERT infers that the red coloring matter is either only soluble in chloroform, or that it is not formed until the chloroform is added.

BAUMERT found this test of great value in deciding whether or not the substance which he found was colchicine. The putrefactive product did not respond to the test.

Some of this substance was sent to BRIEGER, who

decided that it was not a base, but a peptone-like substance. It was also found to be inert physiologically.

Before these investigations were made by BAUMERT, LIEBERMANN had found the same or a similar colchicine-like substance in the cadaver. His description differed from that of BAUMERT only in regard to the taste of the substance, LIEBERMANN having failed to observe any marked taste in the substance which he found, while, as has been stated, BAUMERT reported a distinctly bitter taste.

A colchicine-like substance has been found in beer, and it has been suggested that it was this which the above-mentioned toxicologists found in the bodies which they examined, but LIEBERMANN states that the man whose body he examined had been a total abstainer from beer.

TAMBA compared the reactions of ptomaines obtained from putrid sausage with similar reactions of various alkaloids, and then ascertained the effect upon the alkaloidal reactions by mixing the alkaloids with the ptomaines. His results are as follows:

MORPHINE.—Ptomaines are colored yellow with nitric acid; reddish-yellow with concentrated sulphuric acid; blue, violet, then green with FRÖHDE'S reagent; yellow when evaporated with concentrated sulphuric acid, then treated with hydrochloric acid and decomposed with sodium bicarbonate. The ptomaines reduce ferric chloride, but not iodic acid. With sugar and concentrated sulphuric acid, they give a yellow coloration.

Mixtures of the ptomaines and morphine give absolutely characteristic reactions for morphine with sugar and sulphuric acid, the violet coloration appearing distinctly; and by evaporation on the water-bath with sulphuric acid, addi-

tion of hydrochloric acid and decomposition with sodium bicarbonate, the violet color appearing. Iodic acid is reduced by morphine in the presence of ptomaines, only when the ptomaines are present in minute quantity.

The other reactions for morphine are not applicable in the presence of ptomaines.

STRYCHNINE.—The characteristic color reaction for this alkaloid, with potassium bichromate and sulphuric acid, is not affected by the presence of ptomaines.[1]

BRUCINE.—The nitric acid reaction for brucine is not affected by ptomaines. On the other hand, the reaction with sulphuric and nitric acids, in which a red coloration is obtained, is scarcely visible in the presence of ptomaines. The action of mercuric nitrate and heat on brucine, by which a violet coloration is produced, is not destroyed by the presence of ptomaines.

VERATRINE.—The characteristic coloration of veratrine by concentrated sulphuric acid is not influenced by ptomaines. The same is true of the cherry-red coloration with concentrated hydrochloric acid. On the contrary, the action of sugar and sulphuric acid on veratrine is without result in the presence of ptomaines.

ATROPINE. — The deep violet coloration produced by fuming nitric acid, subsequent concentration, and the addition of alcoholic potassium hydrate, is not affected by the presence of ptomaines. On the other hand, the characteristic odor produced by the action of sulphuric acid and heat on atropine is scarcely recognizable when ptomaines are present.

[1] In contradiction to this, see page 115.

NARCEINE.—The blood-red color produced by concentrated sulphuric acid fails in the presence of ptomaines.

COLCHICINE—Fuming nitric acid colors the ptomaines reddish-yellow, but the violet coloration of colchicine with nitric acid appears in well-defined form, even in the presence of ptomaines. The other reactions for colchicine are valueless when ptomaines are present.

CODEINE.—The blue coloration of codeine with concentrated sulphuric acid holds good when ptomaines are present. The same is true of the reaction with sulphuric acid, heat, and the subsequent addition of nitric acid. FRÖHDE'S reagent fails with codeine when mixed with ptomaines, inasmuch as the bluish coloration rapidly passes into a brown.

ACONITINE.—Phosphoric acid and concentrated sulphuric acid are without reaction on the alkaloid when mixed with ptomaines.

PICROTOXINE.—The reducing action of picrotoxine on alkaline copper sulphate solution is seriously affected by the presence of ptomaines. The same is true of other tests for this poison.

DELPHININE.—The reaction of delphinine with sulphuric acid and bromine water, as well as the one with FRÖHDE'S reagent, is so much influenced by the presence of ptomaines that the alkaloid cannot be recognized.

These results are to be accepted with caution, as it is not reasonable to suppose that all ptomaines will affect the test for the vegetable alkaloids in the same manner, or to the

same degree. Moreover, there is no proof that TAMBA worked with pure ptomaines.

TAMBA has also proposed to separate vegetable from putrefactive alkaloids by adding to ethereal solutions of mixtures an equal volume of a saturated ethereal solution of oxalic acid, and allowing to stand, when the oxalates of the vegetable alkaloids will separate in crystalline form, and the oxalates of the ptomaines will remain in solution. In other words, the oxalates of the vegetable alkaloids are insoluble in ether, while the oxalates of the putrefactive alkaloids are soluble in ether. But, in contradiction to this, BOCKLISCH states that the oxalate of cadaverine is insoluble in ether.

CHAPTER V.

METHODS OF EXTRACTING PTOMAINES.

From what has been given in the preceding pages, one may gather some idea of the peculiar difficulties with which the chemist has to contend in his endeavors to isolate the basic products of putrefaction. He has to deal with very complex substances, of the nature and reactions of many of which he must be ignorant. Besides, the substances which he seeks are often most prone to undergo decomposition, and in this way escape detection. Many ptomaines are volatile or decomposable at any temperature near that of boiling water. In these cases, solutions cannot be evaporated in the ordinary way and the poison separated from the residue. Indeed, the investigator has frequently been disappointed when on the evaporation of a solution, which he has demonstrated to be poisonous, he finds that the residue is wholly inert. Again, he may destroy the ptomaine by the action of reagents which he uses. So simple a procedure as the removal of a metallic base from a solution containing a ptomaine by precipitation with hydrogen sulphide gas has been known to destroy wholly the ptomaine. Probably the most perplexing difficulty in the isolation of these putrefactive alkaloids lies in the great number, complexity, and diversity of the other substances present in the decomposing mass. The same ptomaine may be present in equal quantities in two samples of milk, and yet it may be easily obtained from the one, while from the other only minute traces can be secured. The difference is

due to the fact that the other constituents of the milk in the two samples are at different stages of the putrefactive process, and, consequently, differ greatly in their reactions and in their effects upon the agents employed to isolate the poison. All chemists will appreciate these difficulties.

One of the first things for the chemist who undertakes this work to do, is to ascertain whether or not his reagents are pure. We have found a number of samples of German ether, which was imported on account of its supposed purity, to yield on spontaneous evaporation a residue which gave several of the alkaloidal reactions, and a few drops of which, injected under the skin of a frog, caused paralysis and death within a few minutes. We would advise that 500 c. cm. of the ether to be used should be allowed to evaporate spontaneously, and its residue, if there be one, be examined both chemically and physiologically. The basic substance which exists in some samples of sulphuric ether is pyridine.

GUARESCHI and MOSSO found commercial alcohol almost invariably to contain small quantities of an alkaloidal substance, the odor of which is similar to that of nicotine and pyridine. Its solutions are precipitated by gold chloride, phosphowolframic acid, phosphomolybdic acid, potassium iodide, and MAYER'S reagent, but not by platinum chloride, or tannic acid. It does not reduce, or reduces feebly, ferric salts. From one sample of alcohol they obtained a base which, in addition to the above reactions, did give a precipitate with platinum chloride. Alcohol may be freed from these substances by distillation over tartaric acid.

In amylic alcohol, HAITINGER has found as much as 0.5 per cent. of pyridine. It may be purified in the same manner as recommended for ethylic alcohol.

Chloroform, when found to leave any residue on evapora-

tion, should be washed first with distilled water, then with distilled water rendered alkaline with potassium carbonate, then dried over calcium chloride and distilled.

Petroleum ether sometimes contains a base which has an odor similar to trimethylamine or pyridine, and which gives a precipitate with platinum chloride forming in octahedra.

Benzole may contain a similar substance.

The following methods have been used for the purpose of extracting the putrefactive alkaloids:

THE STAS-OTTO METHOD.—This method depends upon the following facts: (1) the salts of the alkaloids are soluble in water and alcohol, and generally insoluble in ether, and (2) the free alkaloids are soluble in ether, and are removed from alkaline fluids by agitation with ether. These principles are capable of great variety in their application. The usual directions are as follows: Treat the mass under examination with about twice its weight of pure ninety per cent. alcohol, and from ten to thirty grains of tartaric or oxalic acid, digest the whole for some time at about 70°, and filter. Evaporate the filtrate at a temperature not exceeding 35° either in a strong current of air or in vacuo over sulphuric acid. Take up the residue with absolute alcohol, filter, and again evaporate at a low temperature. Dissolve this residue in water, render alkaline with sodium bicarbonate, and agitate with ether. After separation remove the ether with a pipette, or by means of a separator, and allow it to evaporate spontaneously. The residue may be further purified by redissolving in water and again extracting with ether.

The following modifications of this method are employed: instead of tartaric or oxalic acid, acetic acid is frequently used.

When the fluid suspected of containing a ptomaine is already acid from the development of lactic or other organic acid, the addition of an acid is often dispensed with.

Ether extracts are made from both acid and alkaline solutions.

Chloroform, amylic alcohol, and benzene are used as solvents after extraction with ether.

The modification of this method as carried out by SELMI and MARINO-ZUCO is given in detail as follows:

The material is divided as minutely as possible, placed in a large flask and treated with twice its volume of 90 per cent. alcohol, and acidulated with tartaric acid in the proportion of 0.5 gram to 100 c. cm. of the mixture, taking care from time to time that the reaction is permanently acid. The flask, which is connected with a reflux condenser, is now placed on the water-bath and kept at the constant temperature of 70° for twenty-four hours. While yet warm the liquid is transferred to a special apparatus for filtration by the aid of atmospheric pressure. The liquid is poured upon a wet cloth supported upon a perforated porcelain funnel, which is connected below with a receiver exhausted by a water-pump or aspirator. In this way rapid filtration is secured, and by repeated washing the extraction is made thorough. The acid alcoholic liquid is now transferred to a special distillation apparatus.

A large tubulated retort of ten liters capacity is connected by means of cork to a large tubulated receiver. The tubulure of the retort is provided with a small perforated cork which carries a glass tube finely drawn out and extending to the bottom of the retort. The tubulure of the receiver is connected with LIEBIG'S bulbs containing dilute sulphuric acid (1 to 10), and the bulbs in turn are connected with a water-pump or aspirator.

In order to prevent the passage of air through the corks, they are covered with animal membrane which has been freed from fat. By means of the aspirator a fine current of air is drawn through the liquid and suffices to keep it constantly agitated. The retort is kept on the water-bath at a temperature of from 28° to 30°. The receiver is kept cold by a current of water. In this manner the distillation of the alcohol goes on rapidly and conveniently. Moreover, decomposition is so far prevented that volatile bases are never found in the bulbs.

The aqueous residue, after the removal of the alcohol by distillation, is filtered and extracted with ether as long as anything is dissolved. It is then mixed with powdered glass and evaporated to dryness in vacuo. This residue is repeatedly extracted with absolute alcohol. The alcohol is distilled again in the apparatus already described. The residue is taken up with distilled water and filtered. It is then made alkaline with sodium bicarbonate and repeatedly extracted with ether, benzene, and chloroform.

In order to obtain the base from the solvent, the greater part may be evaporated on the water-bath and the remainder allowed to evaporate spontaneously, or the remainder may be treated with dilute hydrochloric acid and the evaporation continued on the water-bath or in vacuo.

Dragendorff's Method. — The finely divided substance is digested for some hours with water acidulated with sulphuric acid at from 40° to 50°. This is repeated two or three times and the united, filtered extracts are evaporated to a syrup. This is treated with four volumes of alcohol and digested for twenty-four hours at 30°. After cooling the alcoholic extract is filtered, the residue washed with 70 per cent. alcohol, and the united filtrates freed

from alcohol by distillation. The aqueous residue diluted if desirable is filtered and submitted to the following extractions:

(1) The acid liquid is shaken with freshly rectified petroleum ether as long as this reagent leaves any residue on evaporation.

(2) The acid fluid is now extracted with benzene.

(3) The next solvent used is chloroform.

(4) The liquid is now again extracted with petroleum ether in order to remove traces of benzene and chloroform.

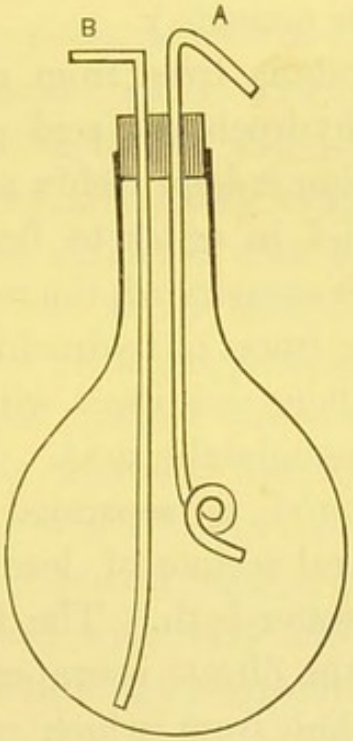
(5) The liquid is now made alkaline with ammonia and successively extracted with petroleum ether, benzene, chloroform, and amylic alcohol.

(6) The remainder of the ammoniacal liquid is mixed with powdered glass, evaporated to dryness, the residue pulverized, and extracted with chloroform.

The residue obtained with each of the above solvents should be examined for ptomaines.

Brieger's Method.—The substance under examination is divided as finely as possible, and then heated with water slightly acidified with hydrochloric acid. During the heating care must be taken that the feebly acid reaction is maintained. The heating should continue for only a few minutes. The liquid is then filtered and concentrated at first on a plate and then on the water-bath to a syrup. If one has material which is highly odorous, as is the case frequently both with aqueous and alcoholic extracts of putrid material, Brieger recommends that a piece of apparatus devised by Bocklisch be used. The fluid to be evaporated is placed in a globular flask, the rubber stopper of which carries two small glass tubes. One of these (b) extends to the bottom of the flask, while (a) terminates just

above the surface of the liquid. The tube (a) is connected with a water-pump or aspirator, which draws the vapor through the tube. In order to prevent the return of condensed fluids, the end of (a) in the flask is curved upon itself. The tube (b) is finely drawn out and through it a current of air is constantly moving. This prevents the formation of a deposit or a pellicle in the fluid. By regu-



lating the amount of air coming through this tube, more or less of a vacuum will be formed in the flask. After evaporation to a syrup, an extraction is made with 96 per cent. alcohol, and the filtered extract is treated with a warm alcoholic solution of lead acetate. The lead precipitate is removed by filtration, the filtrate evaporated to a syrup and again extracted with 96 per cent. alcohol. The alcohol is driven off; the residue taken up with water; traces of lead removed with hydrogen sulphide; and the filtrate, acidified with hydrochloric acid, evaporated to a syrup. This syrup is extracted with alcohol, and the filtrate pre-

cipitated with an alcoholic solution of mercuric chloride. The mercury precipitate is boiled with water, and on account of differences in solubility of the double compounds with mercury, one ptomaine may be separated from others at this stage of the process. (If thought best, the lead precipitate may be freed from lead and carried through the following steps of the process. BRIEGER has found small amounts of ptomaines in the lead precipitate only in his work with poisonous mussels.)

The mercury filtrate is freed from mercury, evaporated, and the excess of hydrochloric acid carefully neutralized with soda (the reaction is kept feebly acid), then it is again taken up with alcohol in order to free it from inorganic salts. The alcohol is evaporated, the residue taken up with water, the remaining traces of hydrochloric acid neutralized with soda; the whole acidified with nitric acid, and treated with phosphomolybdic acid. The phosphomolybdate double compound is separated by filtration, and decomposed by neutral acetate of lead. This is hastened by heating on the water-bath. The lead is removed by hydrogen sulphide, the filtrate is evaporated to a syrup and taken up with alcohol, from which many ptomaines are deposited as chlorides, or double salts may be formed in the alcoholic solution. BRIEGER states that the chlorides as deposited from the alcoholic solution are seldom pure, and he advises, for their purification, precipitation with gold chloride, platinum chloride, or picric acid, and, on account of differences in solubility of these double salts, the process of purification is rendered more easy. The chloride of the base is obtained by removing the metallic base with hydrogen sulphide; while the picrate is taken up with water, acidified with hydrochloric acid, and repeatedly extracted with ether, in order to remove the picric acid.

THE METHODS OF GAUTIER AND ETARD.—The putrid matters, liquid and solid, are distilled at a low temperature in vacuo. The distillate (A) contains a considerable quantity of ammonium carbonate, some phenol, skatol, trimethylamine, and the volatile fatty acids. The residue after distillation is treated in succession by ether and by alcohol.

The extraction with ether (B) separates the ptomaines and some fatty acids. The alcoholic extract (C) removes the remainder of the fatty acids, as well as the acid and neutral nitrogenized bodies, almost all of which are crystallizable. The insoluble residue is boiled with dilute hydrochloric acid, with exclusion of air, finally evaporated to dryness, and the residue again extracted with alcohol. This new alcoholic solution (D) can be divided by acetate and subacetate of lead into two principal portions.

By operating in this manner the complex products of putrefaction are readily separated into four portions.

In his more recent work, GAUTIER has employed the following method: The putrid liquids, after the removal of fats, are feebly acidified with very dilute sulphuric acid, then distilled in vacuo at a low temperature. The distillate contains ammonia, phenol, indol, and skatol. The syrupy residue, separated from any crystals which may have formed, is rendered alkaline with baryta, filtered, and extracted a great number of times with chloroform, in order to dissolve the bases. The solution is distilled at a low temperature, either in vacuo or in a current of carbonic acid. The contents of the retort, on being treated with water and tartaric acid, separate into a brown resin and a liquid portion. The latter is removed and treated with a dilute solution of potash, when it gives off the odor of carbylamine, which was discovered by GAUTIER in 1866, and which, according to CALMEL, is a constituent of the venom of toads. The

alkali also sets free the bases, which are removed by extraction with ether, and the ether evaporated in a current of carbonic acid gas under slight pressure, then under a bell-jar over caustic potash. The bases may be separated by fractional precipitation with platinum chloride, or, if present in sufficient quantity, by distillation in vacuo.

Still later, GAUTIER has modified his method as follows; The alkaline putrid liquid is treated with oxalic acid (instead of sulphuric acid) to free acidulation and as long as the fatty acids continue to separate. The liquid is then warmed and distilled as long as a turbid fluid passes over. Pyrrol, skatol, phenol, indol, volatile fatty acids, and some of the ammonia pass over. The portion which remains in the retort is rendered alkaline with lime water. The precipitate which forms, and which contains the greater part of the fixed fatty acids, is removed. The liquid portion, which is alkaline, is distilled to dryness, care being taken to receive the distillate in very dilute sulphuric acid. The bases and ammonia pass over. The distillate is neutralized (with sulphuric acid) and evaporated almost to dryness, then decanted from ammonium sulphate, which crystallizes. The mother-liquor is extracted with concentrated alcohol, which dissolves the sulphates of the ptomaines. After driving off the alcohol, the residue is rendered alkaline with caustic soda, and successively extracted with ether, petroleum ether, and chloroform.

The lime precipitate is dried and extracted with ether of thirty-six degrees, which removes any fixed bases that may be present.

REMARKS UPON THE METHODS.—The fundamental difference between the STAS-OTTO and the DRAGENDORFF methods consists in the fact that in the former the first

extraction is made with a dilute solution of an organic acid (tartaric usually), while in the second a similar solution of a mineral acid (sulphuric) is employed. In their various modified forms any solvent may be used for separating the alkaloid from the other constituents of the original solution. Therefore, the question has been asked, Which is the more suitable acid for use in making the first solution? The answer to this question will also be the one to the question, Which is the better method of extracting ptomaines, the STAS-OTTO method or that of DRAGENDORFF? The Italian chemists GUARESCHI and MOSSO have attempted to answer this question experimentally, and the evidence which they have furnished is condemnatory of the method of DRAGENDORFF. They show that basic bodies are formed by the action of the dilute sulphuric acid upon albuminous substances. As this point is of vital importance to the investigator in this branch of chemical science, we will give a brief abstract of the work of GUARESCHI and MOSSO:

One kilogram of fresh meat was treated with dilute sulphuric acid (in the proportion recommended in the DRAGENDORFF method) and alcohol. The dark solution after filtration was made alkaline with ammonium hydrate and extracted with ether. The ethereal solution gave on evaporation an oily substance which had the odor of extracts obtained from putrid fibrin. This substance, which was obtained in considerable quantity, was soluble in water and strongly alkaline in reaction. After neutralization with hydrochloric acid, its aqueous solutions gave the following alkaloidal tests:

(1) With platinum chloride, a yellowish-red precipitate, insoluble in water, alcohol, and ether, and apparently identical with the compound obtained from putrid fibrin with the same reagent.

(2) With gold chloride, yellow precipitate, then reduction to metallic gold.

(3) With phosphomolybdic acid, a heavy, yellow precipitate, forming a blue solution on the addition of ammonium hydrate.

(4) With phosphotungstic acid, a white precipitate.

(5) With MAYER'S reagent, a heavy, whitish precipitate.

(6) With picric acid, white precipitate, instantly.

(7) With iodine in potassium iodide solution, a heavy kermes-red precipitate.

(8) With tannic acid, white precipitate.

(9) With mercuric chloride, white, amorphous precipitate.

(10) With MARMÉ'S reagent, heavy precipitate.

(11) With potassium ferricyanide, no precipitate, but a cloudiness, with the formation of Prussian blue on the addition of ferric chloride.

The same quantity of this meat was also treated by the STAS-OTTO method. The alcoholic extract was evaporated on the water-bath and not in vacuo. The acid was neutralized with sodium bicarbonate. The ether extract gave on evaporation a faintly yellow residue, of not unpleasant odor and feebly alkaline in reaction. After neutralization with hydrochloric acid, it was only slightly soluble in water. The pale yellow filtrate gave no precipitate with Nos. 1, 2, 8, 9, and 10 of the above mentioned reagents, but gave a slight turbidity with Nos. 3, 4, 5, 6, and 7, and with 11 formed Prussian blue.

GUARESCHI and MOSSO conclude from this and other experiments that the DRAGENDORFF method is not suitable for the extraction of ptomaines, and they recommend the employment of the STAS-OTTO method with these con-

ditions: (1) no more acid should be added than is absolutely necessary to keep the reaction acid; (2) the heat used in evaporation should not be great, and it is better that evaporation should be made in vacuo. In this way, they say, no ptomaine will be obtained from fresh tissue.

The same investigators extracted fresh flesh without the addition of any acid. Thirty kilograms of perfectly fresh meat were digested for two hours at from 50° to 60° with about one and one-half volumes of water. The fluids of the meat contained enough acid to give to the whole of this solution an acid reaction. It was evaporated to half its volume on the water-bath, filtered, and evaporated still further. The small residue was taken up with about four volumes of 96 per cent. alcohol. The reddish, alcoholic solution left on evaporation on the water-bath a brownish residue, which was dissolved in water and extracted with ether (A), then the solution was made alkaline with ammonium hydrate and again extracted with ether (B).

(A) gave on evaporation and cooling crystals of methyl-hydantoin, while the mother liquor contained acetic acid.

(B) also yielded crystals of methyl-hydantoin, while the mother liquor gave alkaloidal reactions with most of the general alkaloidal reagents, none with platinum chloride. Methyl-hydantoin does not give these reactions.

Marino-Zuco has made many comparative tests with these two methods. He ascertained that by treating fresh eggs, brain, liver, spleen, kidney, lungs, heart, and blood by either of the methods, he could obtain a substance which gave alkaloidal reactions, and which he demonstrated to be choline. His experiments led him to believe that choline did not exist preformed in these fresh tissues, but that it resulted from the action of the dilute acids upon lecithin. It was found most abundantly in those tissues which are

rich in lecithin, such as the yolks of eggs, brain, liver, and blood; while only traces could be obtained from the whites of eggs, lungs, and heart. The method of DRAGENDORFF was found to furnish much larger quantities of choline than could be obtained by the STAS-OTTO method.

COPPOLA agrees with his countrymen, mentioned above, in condemning the method of DRAGENDORFF.

Enough has been said to show that results obtained by the STAS-OTTO method are much more reliable than those secured by the method of DRAGENDORFF. However, the former is not a perfect method, nor has a perfect one yet been devised. The principal difficulties met with in the STAS-OTTO method are as follows:

(1) In most instances the extraction of the base is very incomplete. (2) The degree to which the putrefactive alkaloid is removed by the solvent will depend very largely upon the nature of the other substances present. This fact in some cases aids and in others hinders the labors of the investigator. Thus, several ptomaines, which when pure are wholly insoluble in ether, may be removed, in part at least, from organic mixtures by this solvent by passing into the solution along with other substances, but if the attempt is made to purify one of these bases by repeated solution and extraction with ether, the result is a failure, because the more perfectly the alkaloid is freed from impurities, the less soluble it is in ether. This criticism, however, is equally applicable to the DRAGENDORFF method, and to all others in so far as extractions are made.

However, we may state that whenever it is applicable this method is the best now employed. By it the substances are submitted to the least chemical manipulation, and the results obtained are the most reliable. Many of the more complex putrefactive products are so easily de-

composed or otherwise altered that the investigator should seek to isolate them by the simplest methods possible. If it can be done without the addition of any acid or without the application of heat, so much the better.

Especially is the modification of this method employed by MARINO-ZUCO, and already described, to be commended.

By his method, BRIEGER has discovered a considerable number of basic bodies and has given great impetus to the study of the chemistry of putrefaction. The method is capable of a great many modifications. As long ago as 1868, BERGMANN and SCHMIEDEBERG employed precipitation with metallic salts in order to obtain sepsine from putrid yeast. The method used by them was as follows: Putrid yeast was diffused through parchment paper; the diffusate was acidified with hydrochloric acid, and treated with mercuric chloride solution until a heavy cloudiness and, after some time, a slight precipitate formed. This was removed by filtration; the filtrate was rendered strongly alkaline with sodium carbonate, and then further treated with a solution of mercuric chloride as long as a precipitate formed. This precipitate was collected on a filter, washed, suspended in a little acidified water, and decomposed with hydrogen sulphide. The precipitate was removed, the free hydrochloric acid in the filtrate taken up with silver carbonate and the excess of silver removed with hydrogen sulphide. The filtrate was evaporated to dryness; the residue dissolved in alcohol (a part remaining insoluble) and acidified with sulphuric acid, when a colorless, or slightly yellow crystalline precipitate formed. The crystalline sepsine sulphate was purified by solution in water and precipitation with alcohol.

BRIEGER has obtained some of his bases by a much simplified modification of his complete method, which we have

given in full. For instance, in obtaining neuridine, he treated the aqueous extract of the putrid material after boiling and filtration with mercuric chloride, collected the precipitate, decomposed it with hydrogen sulphide, evaporated the filtrate on the water-bath, and extracted the base from the residue with dilute alcohol.

By this method and its modifications BRIEGER has obtained many brilliant results, among which may be mentioned his discovery of mytilotoxine, typhotoxine, and tetanine. However, the method is not free from criticism. The great number of chemical manipulations to which the organic matter is subjected is liable to lead to the formation of some basic substances and to the destruction of others. One is justified in considering the isolated base as pre-existing in the original material only when it produces symptoms identical with those caused by the substance from which it is extracted. There can be no doubt that by this method many ptomaines would be decomposed. With it EHRENBERG obtained from poisonous sausage only inert bases, and tyrotoxicon, the ptomaine of poisonous cheese, is decomposed both by heat and the hydrogen sulphide employed. The origin of the ptomaines possessing a muscarine-like action discovered by BRIEGER has been questioned by GRAM, who states that when the lactate of choline, an inert substance which is widely distributed both in plants and animals, is heated, it is converted into a poison with such an action (see page 190).

CHAPTER VI.

CHEMISTRY OF THE PTOMAINES.

The basic substances described in the following pages are arranged, so far as possible, in the regular natural order. An inspection of the list of these bases will show the remarkable fact of the predominancy of the amine type. Almost two-thirds of the known ptomaines contain only C, H, and N, and represent simple ammonia substitution compounds. Of the oxygenated bases all of those whose constitution is known possess the trimethylamine molecule as their basic constituent, and it is quite probable that most, if not all, of the remaining ptomaines will be found to possess the same or a similar basic nucleus.

It will be seen, furthermore, that a very large number of the ptomaines described possess little or no toxic action, and are, therefore, physiologically inert. It would seem, as Brieger has already pointed out, that a certain quantity of oxygen is necessary to the formation of poisonous bases. A free supply of oxygen, on the other hand, invariably yields non-toxic ptomaines.

Methylamine, $CH_3.NH_2$. — This is the simplest organic base that is formed in the process of putrefaction. It is ammonia in which one atom of hydrogen has been replaced by the methyl radical. It occurs in herring-brine (Tollens, 1866; Bocklisch, 1885); in decomposing herring, twelve days in spring (Bocklisch); in pike, six days in summer (Bocklisch); in haddock, two months at

a low temperature (BOCKLISCH); in the fermentation of choline chloride (HASEBROEK). BRIEGER has shown it to be present in cultures of comma bacillus on beef-broth which were kept for six weeks at 37°–38°. In BRIEGER'S method, methylamine is found both in the mercuric chloride precipitate and filtrate. The mercury double salt is readily soluble in water, and can thus be separated from any accompanying cadaverine or putrescine. Methylamine is an inflammable gas of strong ammoniacal odor, and burning with a yellow flame. It is readily soluble in water, and its solutions give reactions similar to those of ammonia. Its salts are, as a rule, also soluble in both water and alcohol.

The HYDROCHLORIDE, $CH_3.NH_2.HCl$, crystallizes in large deliquescent plates. On being heated with alkali, it gives off the odor of methylamine.

The PLATINOCHLORIDE, $(CH_3.NH_2.HCl)_2PtCl_4$ (Pt = 41.68 per cent.), yields hexagonal plates which usually occur heaped up in several layers. It is soluble in about fifty parts of water at ordinary temperature, and can be readily recrystallized from hot water. It is insoluble in absolute alcohol and in ether.

The AUROCHLORIDE, $CH_3.NH_2.HCl.AuCl_3 + H_2O$, forms prisms, which are readily soluble in water. There is also a readily soluble picrate.

Methylamine does not possess any toxic action, even when given in fairly large doses. This physiological indifference is shared by nearly all the monamines and diamines that have been obtained among the products of putrefaction.

DIMETHYLAMINE, $(CH_3)_2.NH$, has been found in putrefying gelatine, ten days at 35° (BRIEGER); in yeast decomposing in covered vessels for four weeks during summer (BRIEGER); in decomposing perch, six days in summer

(Bocklisch); and in herring-brine (Bocklisch). It is also formed, together with trimethylamine, when neuridine hydrochloride is distilled with sodium hydrate (Brieger, I., 23). It occurs in the mercuric chloride precipitate as well as filtrate. From cadaverine it can be separated by platinum chloride, since cadaverine platinochloride is difficultly soluble in cold water, and recrystallizes from hot water, whereas the dimethylamine double salt remains in the mother liquor. In like manner it can be separated from neuridine. From choline it can be isolated by recrystallizing the mercuric chloride precipitate from hot water.

The free base is a gas at ordinary temperature, but can be condensed to a liquid which boils at 8°–9°. The hydrochloride, $(CH_3)_2.NH.HCL$, crystallizes in needles, which deliquesce on exposure to air and are soluble in absolute alcohol (Brieger, I., 56). It is insoluble in absolute alcohol (Bocklisch) but soluble in chloroform (Behrend), and can then be separated from methylamine hydrochloride, which is insoluble in chloroform.

The Platinochloride, $[(CH_3)_2.NH.HCl]_2PtCl_4$, (Pt = 39.36 per cent.), crystallizes in long needles, which are easily soluble in hot water, less soluble in cold water. Sometimes it forms orange-yellow plates or prisms, or else small needles.

The Aurochloride, $(CH_3)_2.NH.HCl.AuCl_3$, forms needles (Bocklisch) which are insoluble in absolute alcohol, or large yellow monoclinic plates (Hjortdahl).

Trimethylamine, $(CH_3)_3N$, has been for a long time known to occur in animal and vegetable tissues. Dessaignes showed its presence in leaves of Chenopodium (1851), in the blood of calves (1857), and later in human urine. It has been obtained from ergot (Secale cornutum)

by WALZ (1852) and BRIEGER (1886); from herring-brine by WERTHEIM, WINKLES, TOLLENS, and BOCKLISCH, and from cultures of the comma bacillus by BRIEGER. In these substances, with the exception of herring-brine, it probably does not exist preformed, but is rather a product of the method employed for its isolation. In fact, BRIEGER has shown that it does not exist in ergot, but is formed at the expense of the choline present, which, on distillation with potash, decomposes and yields trimethylamine. It may have a similar origin in most of the other cases, since choline is now known to be widely disseminated in plants and animals, either as such or as a constituent of the more complex lecithin. Trimethylamine has been found in the putrefaction of yeast (HESSE, 1857; MÜLLER, 1858); in cheese after six weeks in midsummer (BRIEGER); in human liver and spleen after from two to seven days (BRIEGER); in perch after six days in midsummer (BOCKLISCH); in mussel (Mytilus edulis) after sixteen days (BRIEGER); in putrefying brains after from one to two months, and in fresh brains (GUARESCHI and MOSSO); and in cultures of the Streptococcus pyogenes on beef-broth, bouillon, meat extract, and blood-serum (BRIEGER). It is also formed when choline, betaine, or neuridine is distilled with potash.

Trimethylamine is found both in the mercuric chloride precipitate and filtrate. It remains in the mother liquor from which cadaverine, neuridine, and dimethylamine platinochlorides have crystallized. If an aqueous solution of mercuric chloride is used as the precipitant, the trimethylamine will be found almost entirely in the filtrate, from which it can be obtained after removal of the mercury by evaporating the filtrate to dryness, extracting

with alcohol and treating the solution thus obtained with alcoholic platinum chloride.

The free base is a liquid possessing a strong, fish-like odor. Its boiling point is 9.3°. It is strongly alkaline in reaction and freely soluble in water.

The HYDROCHLORIDE, $(CH_3)_3N.HCl$, is deliquescent and freely soluble in water and alcohol. Heated to 285° it decomposes. With alkalies it gives off the odor of the free base.

The PLATINOCHLORIDE, $[(CH_3)_3N.HCl]_2PtCl_4$ (Pt = 37.25 per cent.), is soluble in hot water, from which, on cooling, it recrystallizes in orange-red octahedra or needles, which do not lose water when heated at 100°–110° (BOCKLISCH).

The AUROCHLORIDE, $(CH_3)_3N.HCl.AuCl_3$ (Au = 49.37 per cent.), is easily soluble, and hence can be separated from choline aurochloride, which is difficultly soluble. Similarly, this base can be separated from ammonia by the use of gold chloride.

Trimethylamine is not a strong poison, since very large doses of it must be given in order to bring out any physiological disturbances.

ETHYLAMINE, $C_2H_5.NH_2$, is formed in putrefying yeast (HESSE, 1857); in wheat flour (SULLIVAN, 1858); and also in the distillation of beet-sugar residues.

It is a strongly ammoniacal liquid boiling at 18.7°, and is miscible with water in every proportion. Like the other amines, it is combustible. It possesses strong basic properties, and is capable of expelling ammonia from its salts in a manner analogous to the action of the fixed alkalies.

The HYDROCHLORIDE, $C_2H_5.NH_2.HCl$, forms deli-

quescent plates, which melt at 76°–80°. It is readily soluble in water and alcohol.

The PLATINOCHLORIDE, $[C_2H_5.NH_2.HCl]_2PtCl_4$, forms orange-yellow rhombohedra (WELTZIEN), or hexagonal-rhombohedral crystals (TOPSOË).

The AUROCHLORIDE, $C_2H_5.NH_2.HCl.AuCl_3$, forms gold-yellow monoclinic prisms, readily soluble in water.

With picric acid it forms short brown prisms, not very soluble in water.

DIETHYLAMINE, $(C_2H_5)_2NH$, has been obtained by BOCKLISCH from pike which were allowed to putrefy for six days in summer.

It is an inflammable liquid which boils at 57.5°, possesses strong basic properties, and is soluble in water.

The HYDROCHLORIDE, $(C_2H_5)_2NH.HCl$, crystallizes in needles (BOCKLISCH); in long needles and prisms from absolute alcohol; in plates from ether-alcohol. These are not deliquescent and are easily soluble in water and in chloroform; rather difficultly in absolute alcohol. Heated with sodium hydrate it gives off alkaline vapors. From an alcoholic solution it is precipitated by addition of alcoholic mercuric chloride. The mercury double salt is difficultly soluble in hot water, from which it recrystallizes on cooling.

The PLATINOCHLORIDE, $[(C_2H_5)_2.NH.HCl]_2PtCl_4$, crystallizes in orange-yellow monoclinic crystals, which are easily soluble in water.

The AUROCHLORIDE, $(C_2H_5)_2.NH.HCl.AuCl_3$ (Au = 47.69 per cent), forms trimetric crystals (TOPSOË), which are difficultly soluble (BOCKLISCH). It melts at about 165°.

With picric acid it forms an easily soluble picrate (LEA).

TRIETHYLAMINE, $C_6H_{15}N = (C_2H_5)_3N$, was obtained by BRIEGER from haddock which were exposed for five days

in an open vessel during summer. He obtained it by distilling with potash, after removal of platinum by hydrogen sulphide, the mother liquor from which neuridine, the base $C_2H_8N_2$, muscarine, and gadinine had successively crystallized (see page 204).

The free base is oily in character and possesses an ammoniacal odor. It is but slightly soluble in water, and boils at 89°–89.5°.

The PLATINOCHLORIDE, $[(C_2H_5)_3N.HCl]_2PtCl_4$ (Pt= 32.20 per cent.), crystallizes in needles which are readily soluble in water.

With mercuric chloride the aqueous solution gives no precipitate.

With picric acid it yields yellow needles which are but slightly soluble in cold water.

PROPYLAMINE, $C_3H_7.NH_2$, is isomeric with trimethylamine and can, therefore, be easily confounded with that base. There are two propylamines possible represented by the formulæ $CH_3.CH_2.CH_2.NH_2$ and $(CH_3)_2.CH.NH_2$. The former, or the normal compound, boils at 47°–48°, whilst the latter, or iso-propylamine, boils at 31.5°. Both are liquids possessing an ammoniacal fish-like odor. They form crystalline salts; the hydrochlorides melt respectively at 155°–158°, and at 139.5°.

Iso-propylamine (?) has been found among the distillation products of the vinasse of beet-root molasses. Propylamine has been obtained by BRIEGER from cultures of the bacteria of human fæces on gelatine. SCHWANERT has isolated from the organs of a cadaver a basic substance which was said to possess an odor similar to propylamine.

ISO-AMYLAMINE, $C_5H_{13}N = (CH_3)_2.CH.CH_2.CH_2.NH_2$, has been obtained by LIMPRICHT in the distillation of horn

with potash; it also occurs in the putrefaction of yeast (MÜLLER, HESSE, 1857). It boils at 95°.

CAPROYLAMINE (HEXYLAMINE), $C_6H_{15}N$, has been found by HESSE (1857) to occur in the putrefaction of yeast. HAGER isolated from some putrid material what he thought to be a mixture of amylamine and caproylamine, and named it septicine.

TETANOTOXINE, $C_5H_{11}N$, (?) was obtained by BRIEGER (1887) as one of the products of the growth of the tetanus microbe on beef-broth or on brain-broth. It is tetanizing in its action, produces first tremor, then paralysis and violent convulsions.

SPASMOTOXINE, a base as yet of unknown composition, produces in animals violent clonic and tonic convulsions. It was obtained by BRIEGER (1887) from cultures of the tetanus germ on beef-broth.

Another *toxine* was obtained in cultures of the tetanus microbe which produced a complete tetanus, salivation, and tear secretion. Besides these three bases he isolated another toxic substance, tetanine (page 211).

A BASE, $C_8H_{11}N$, isomeric, but not identical, with aldehyde-collidine, was obtained by NENCKI as early as 1876, by allowing a mixture of 200 grams of pancreas and 600 grams of gelatine in ten litres of water to putrefy for five days at 40°. The method used by NENCKI for its isolation is as follows: The fluid mass was distilled with sulphuric acid, to drive off the volatile acids, then rendered alkaline with barium hydrate, and again distilled. The distillate was received in dilute hydrochloric acid, and on

evaporation gave a crystalline residue of ammonium chloride, and of a salt which formed in long rhombic plates. The latter were separated from the ammonium salt by absolute alcohol. The free base was obtained from the salt by treating it with sodium hydrate, and extracting the solution with ether.

The free base is oily in character, and possesses a peculiar, not unpleasant odor. It readily absorbs carbonic acid gas from the air, forming after a time a lamellar, crystalline mass of the carbonate. The salt of this base on heating gives off an oil which burns with a smoky flame, and possesses an odor similar to that of xylol or cumol. NENCKI is, therefore, of the opinion that the ptomaine is an aromatic base, probably an isophenyl-ethylamine of the following composition: $C_6H_5 - CH\begin{matrix}CH_3\\NH_2\end{matrix}$. He thinks that it may arise from the putrefaction of tyrosin, according to the following equation:

$$C_9H_{11}NO_3 = C_8H_{11}N + CO_2 + O.$$

We know that tyrosin does split up, on being heated to 270°, into carbonic acid and oxyphenyl-ethylamine, thus:

$$C_6H_4\begin{matrix}OH\\CH_2.CH.NH_2.COOH\end{matrix} = C_6H_4\begin{matrix}OH\\CH_2.CH_2.NH_2\end{matrix} + CO_2.$$

In 1883 ERLENMEYER and LIPP observed that phenyl-*a*-amidopropionic acid (phenyl-alanine), on dry distillation, decomposed with the formation, among other products, of a base having the composition $C_8H_{11}N$. This base was found to be identical with phenyl-ethylamine, $C_6H_5.CH_2.CH_2.NH_2$, and in its properties it resembles NENCKI's base, which is isomeric with it. From the fact that phenyl-*a*-amidopropionic acid is a well-known putre-

factive product, it would seem that NENCKI's base may arise either from the putrefactive decomposition of the acid, or from the splitting up of the acid as a consequence of the method employed in isolating the base. The latter would seem to be the most probable explanation of the genesis of this base, inasmuch as BRIEGER, by using his method for the isolation of ptomaines, has not been able to obtain it from putrid gelatine.

The PLATINOCHLORIDE, $(C_8H_{11}N.HCl)_2PtCl_4$ (Pt = 30.16 per cent.), is readily soluble in hot water, and but slightly soluble in cold water, and can be, therefore, recrystallized from water. It forms beautiful, flat needles.

NENCKI also obtained from putrid gelatine, under certain ill-defined conditions, especially when no glycocoll was present, a basic product which gave, with sulphuric acid, large lamellar crystals. The free base forms a thick colorless syrup, possessing a nauseous, bitter taste. It did not become crystalline even after standing some time. Unlike the base $C_8H_{11}N$, it is not volatile, and is, therefore, obtained on evaporation of the acidulated solution after previous removal of the volatile bases by distillation with baryta.

A BASE, $C_8H_{13}N$, was obtained by GAUTIER and ETARD from the chloroformic extracts (see method, page 133) from putrefying mackerel, as well as from the decomposing flesh of the horse and ox. It is regarded by these authors as a constant and definite product of the bacterial fermentation of albuminoid substances; but this view is hardly justifiable, inasmuch as the base has not been found by other investigators. NENCKI (1882) asserted the identity of this base with the one which he had isolated in 1876, and to

which he had ascribed the formula $C_8H_{11}N$. On the other hand GAUTIER and ETARD consider their base to be identical with the hydrocollidine obtained by CAHOURS and ETARD by the action of selenium on nicotine.

The free base is an alkaline, almost colorless, oily liquid, possessing a penetrating odor resembling that of seringa. It is volatile without decomposition and boils at about 205°, whilst hydrocollidine boils at 210°. Its density at zero is 1.0296. When exposed to the air it oxidizes slowly, becomes brown and viscous, and at the same time absorbs carbonic acid. It differs from a collidine in possessing a strong reducing action, since both the gold and platinum double salts become reduced on heating.

The HYDROCHLORIDE, $C_8H_{13}N.HCl$, is very soluble in water and in alcohol, and usually forms fine needles resembling snow crystals. It is neutral in reaction and possesses a bitter taste. In the presence of an excess of acid it reddens and resinifies.

The PLATINOCHLORIDE, $(C_8H_{13}N.HCl)_2PtCl_4$ (Pt = 29.7 per cent.), is of a light yellow, flesh color, crystalline, and but slightly soluble. It dissolves on warming and recrystallizes in bent needles.

The AUROCHLORIDE is rather soluble, and becomes slowly reduced in the cold; rapidly on warming.

PHYSIOLOGICAL ACTION.—This isomer of hydrocollidine is strongly poisonous. Even so small a dose as 0.0017 gram of the hydrochloride produced, when injected under the skin of a bird, marked unsteadiness of gait followed by paralysis of the extremities, and finally death. The pupils are normal and the heart stops in diastole. Larger doses (0.007 gram) cause at first vomiting and staggering, which soon give way to a condition of exaltation. Toward the

end tetanic convulsions set in, followed by almost complete paralysis.

A BASE, $C_9H_{13}N$, isomeric with parvoline, has been extracted by GAUTIER and ETARD (1881) from decomposing mackerel and horseflesh. The method employed by these chemists for its isolation is given on page 134. The identity of this base with the synthetic parvoline, obtained by WAAGE by heating ammonia with propionic aldehyde in a sealed tube at 200°, cannot be considered to be definitely settled, although an apparent identity exists in regard to their boiling points. Thus, the synthetic parvoline boils at 193°–196°, whilst GAUTIER and ETARD assign to their base a boiling point a little below 200°. Further investigation is necessary to decide upon the question of the identity of this base with parvoline, or of the ptomaine $C_8H_{13}N$ with hydrocollidine.

The free base is an oily, amber-colored liquid, possessing the odor of hawthorn blossoms. It is slightly soluble in water; very soluble in alcohol, in ether, and in chloroform. Its boiling point, as stated above, is a trifle below 200°. Like the bases $C_8H_{13}N$ and $C_{10}H_{15}N$ it becomes brown and soon resinifies on exposure to air.

The PLATINOCHLORIDE, $(C_9H_{13}N.HCl)_2PtCl_4$ (Pt = 28.5 per cent.), is slightly soluble, crystalline, and flesh colored; exposed to the air it soon becomes pink.

The AUROCHLORIDE is quite soluble.

A BASE, $C_{10}H_{15}N$, was isolated by GUARESCHI and MOSSO (1883) from ox-blood fibrin which had been allowed to putrefy for five months. In 1886 OECHSNER DE CONINCK found it among the basic products formed in the putrefaction of the jelly-fish (poulpes marins, HUGOUNENQ,

page 21). The method used for its extraction was that of GAUTIER and ETARD (see page 133). It forms a brownish oil of strong alkaline reaction, which soon resinifies. It possesses a weak pyridine or coniine odor, and is but slightly soluble in water.

In regard to the constitution of this ptomaine we know nothing, but from its physical characters it would seem to possess a pyridine nucleus. It is isomeric with corindine, a homologue of parvoline, and collidine, which has been obtained from coal tar.

For the behavior of the hydrochloride to alkaloidal reagents, see Table I.

The HYDROCHLORIDE, $C_{10}H_{15}N.HCl$, crystallizes in colorless cholesterine-like plates which are somewhat deliquescent.

The PLATINOCHLORIDE, $(C_{10}H_{15}N.HCl)_2PtCl_4$ (Pt = 27.49 per cent.), forms a light flesh-colored, crystalline precipitate, and is insoluble in water, alcohol, and ether. It does not resinify and is stable at 100°.

In its physiological action this ptomaine resembles curara, although it is by no means as strong. 0.012 gram of the free base produced in a frog dilatation of the pupil, and slowing of the respiration. The nostrils were motionless, and within five hours complete paralysis of the muscles took place. The reflex excitability gradually diminished until it finally disappeared. An orange-blossom odor was observed about the frogs which were poisoned by this ptomaine. The same amount of ptomaine injected into a green finch produced vomiting, and a condition of weakness and decreased sensibility, followed soon, however, by recovery. A rat was not affected by 0.020 gram of the free base. The hydrochloride acts much more energetically.

Ethylidenediamine (?), $C_2H_8N_2$.—This base was considered at first by Brieger to be identical with ethylenediamine, but subsequent comparison showed this to be an error. Thus, the former is poisonous and does not form a gold salt, whilst the latter is not poisonous and does form a rather difficultly soluble gold salt. Again, ethylenediamine forms a platinochloride which is almost insoluble in hot water, whereas the platinum double salt of the ptomaine is much more easily soluble. Brieger is, therefore, inclined to think that it is identical with ethylidenediamine, $CH_3.CH(NH_2)_2$, rather than with ethylenediamine, which has this structure, $CH_2.NH_2.CH_2.NH_2$. This ptomaine was obtained by Brieger (I., 44) from decomposing haddock (see page 204).

The free base can be obtained, without decomposition, on distilling the hydrochloride with sodium hydrate.

The Hydrochloride, $C_2H_8N_2.2HCl$, crystallizes in long glistening needles which are readily soluble in water, insoluble in absolute alcohol. It gives no combination with gold chloride. For its behavior to alkaloidal reagents see Table I.

The Platinochloride, $C_2H_8N_2.2HCl.PtCl_4$ (Pt. = 41.85 per cent.), forms small yellow plates which are moderately difficultly soluble in water. It can be readily recrystallized from hot water.

Physiological Action.—Frogs seem to be less susceptible to the action of this poison than mice or guinea-pigs. In the latter, it produces a short time after injection an abundant periodic flow of secretion from the nose, mouth, and eyes. The pupils dilate and the eyeballs project. Violent dyspnœa then comes on and predominates until the death of the animal, which does not take place for twenty-four hours or more. The heart is stopped in diastole.

TRIMETHYLENEDIAMINE (?), $C_3H_8N_2$, is a toxic base isolated by BRIEGER (1887) from cultures of the comma bacillus on beef-broth. It is present, however, in exceedingly minute quantity and occurs in the mercuric chloride precipitate, from which it is obtained by the following method: The precipitate is decomposed by hydrogen sulphide, the filtrate evaporated to dryness, and the residue taken up with absolute alcohol and precipitated by an alcoholic solution of sodium picrate. The precipitate thus obtained consists of the picrates of cadaverine, creatinine, and of this new base. It is boiled with absolute alcohol to remove the insoluble cadaverine picrate; the filtrate is evaporated to expel the alcohol, and the bases then converted into the platinum double salts, whereby the easily soluble creatinine platinochloride can be separated from the corresponding less soluble compound of the new base.

Owing to the small quantity of this substance present, a complete study of its properties has not as yet been made. It gives difficultly soluble precipitates with gold chloride and with platinum chloride; the compound with the latter crystallizes in long needles. With picric acid it gives a precipitate consisting of felted needles which resemble creatinine picrate; they melt at 198°. Phosphomolybdic acid yields a precipitate crystallizing in plates, whilst potassium-bismuth iodide gives dark colored fine needles. From its physiological action its seems to be identical with the basic substance isolated from choleraic bodies by different observers. It causes violent convulsions and muscle tremor.

Besides trimethylenediamine, another toxine was obtained by BRIEGER from cholera cultures, but in quantity insufficient for analysis. It was obtained from the mercuric

chloride filtrate after elimination of methylamine, trimethylamine, and traces of choline and creatinine, as an insoluble platinum double salt. Subcutaneous injection of this base into mice produced a paralysis-like lethargic condition, slowing of respiration and heart's action, lowering of temperature, and finally, death in twelve to twenty-four hours. In some cases bloody stools were passed.

PUTRESCINE, $C_4H_{12}N_2$, is a diamine which almost invariably occurs together with cadaverine, with which it is apparently closely related. This base was also discovered by BRIEGER (II., 42), who has obtained it from putrefying human internal organs (for four months at a low temperature without access of much oxygen); and from the same material, decomposing at the ordinary temperature of the room, for from three days to three weeks. It has also been obtained from herring, twelve days in spring; from pike, six days in summer; from haddock, two months (BOCKLISCH). Also from putrid mussel, sixteen days (BRIEGER); and from human as well as horse flesh. BRIEGER has obtained it from cultures of the bacteria of human fæces on gelatine, and in small quantity in rather old cultures of the comma bacillus on beef-broth; in larger quantity in cultures of the same germ on blood serum.

Although putrescine is recognizable on about the fourth day of the putrefaction, yet it does not occur in appreciable quantity until about the eleventh day. The amount that is formed increases as the putrefaction goes on, so that a considerable quantity may be obtained after two or three weeks. A very good source for the preparation of putrescine, cadaverine, and neuridine is gelatine which has been allowed to decompose in contact with water for some weeks. Neuridine is, apparently, formed first, but is soon replaced

by the former two bases. In the process of extraction it is first obtained in the alcoholic mercuric chloride precipitate. For its separation from cadaverine and other accompanying bases, see page 169.

Putrescine (from *putresco*, to rot, to putrefy) is a water-clear, rather thin liquid of a peculiar semen-like odor, reminding one somewhat of the pyridine bases. It absorbs carbonic acid energetically from the air, without losing thereby the repulsive odor. The boiling point of the free base, as ordinarily obtained, is about 135°. It is not decomposed by distillation with potassium hydrate, and is rather difficultly volatile with steam. With acids it forms beautiful crystalline salts. Putrescine unites with water, like ethylenediamine, to form a hydrate, and this water can only be removed by distillation with metallic sodium. The perfectly anhydrous base boils at 156°–157°, and then solidifies to plates. Like cadaverine, it is difficultly soluble in ether.

The constitution of putrescine has not been determined. From its empirical composition and its apparent relation to cadaverine (pentamethylenediamine) it might be supposed to be a butylenediamine (probably tetramethylenediamine). However, on heating the concentrated aqueous solution of the hydrochloride with potassium nitrite there is produced an oil, soluble in water, from which it can be extracted with ether. This oil, on treatment with phenol and sulphuric acid, gives LIEBERMANN'S nitroso-reaction, showing conclusively that putrescine is not a primary diamine (butylenediamine), but is rather a secondary diamine (BRIEGER, II., 42). Again, if it is a primary diamine it should take up, on repeated treatment with methyl iodide, six methyl radicals; whereas, if it is a secondary diamine, only four methyl radicals can enter the

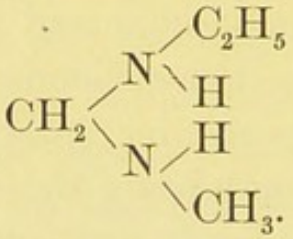
molecule. Thus to illustrate, methylamine, $CH_3.NH_2$ (a primary amine), combines with three molecules of methyl iodide to form $(CH_3)_4N.HI$. Similarly, dimethylamine, $(CH_3)_2.NH$, requires only two molecules to form $(CH_3)_4N.HI$. In the case of diamines, double this number of methyl groups is required to effect complete saturation. As a matter of fact, BRIEGER (III., 101), on treating putrescine with methyl iodide, has succeeded in introducing four, and only four methyl radicals, and hence it follows that putrescine is not a primary amine, but is a secondary amine.

Putrescine, therefore, is not a butylenediamine, nor is it a homologue of cadaverine. From these facts it follows that putrescine possesses one of the subjoined formulæ.

It is either dimethyl-ethylenediamime:

$$\begin{array}{l} CH_2—NH—CH_3 \\ | \\ CH_2—NH—CH_3 \end{array}$$

or, it is methyl-ethyl-methylenediamine:



The tetra-methyl substitution-product of putrescine can be distilled without decomposition. The free base crystallizes in long prisms. The hydrochloride forms small needles which are easily soluble; with phosphotungstic acid it gives a white crystalline precipitate, with phosphomolybdic acid a yellow crystalline precipitate, with picric acid needles. Potassium-bismuth iodide gives a brownish-red amorphous deposit, whilst the potassium mercuric iodide forms prisms. Gold chloride yields difficultly, and

platinum chloride easily soluble octahedra; aqueous mercuric chloride forms needles.

The aurochloride has the formula $C_8H_{22}N_2.2AuCl_4$.

This tetra-methyl derivative of putrescine is enormously poisonous as compared with putrescine. The symptoms are the same as those produced by muscarine or neurine. They are: abundant salivation, dyspnœa; respiration at first increases, then decreases; contraction of the pupils; paralysis of the muscles of the limbs and trunk, increased peristaltic action of the intestines, ejaculation of semen, dribbling of urine, and, finally, violent clonic convulsions. In the case of mice and guinea-pigs, the convulsions are prominent immediately after the injection of the poison.

PUTRESCINE HYDROCHLORIDE, $C_4H_{12}N_2.2HCl$, forms long colorless needles, which are very easily soluble in water; difficultly so in dilute alcohol; entirely insoluble in absolute alcohol, and can thus be separated from cadaverine hydrochloride. To accomplish this separation it is, perhaps, better to dissolve the mixture of the hydrochlorides in hot 96 per cent. alcohol. On cooling the solution thus obtained the putrescine salt crystallizes out, whereas that of cadaverine remains in solution. Putrescine hydrochloride differs from cadaverine hydrochloride, in that it is not hygroscopic, and can be exposed for days to the air without suffering any change on the surface of the crystals.

For the behavior of the free base and the hydrochloride to alkaloidal reagents, see Table I. Putrescine is not toxic, though it possesses some marked physiological properties (see Cadaverine, page 163). It is optically inactive.

The PLATINOCHLORIDE, $C_4H_{12}N_2.2HCl.PtCl_4$ (Pt = 39.52 per cent.), often appears under the microscope in the form of cholesterine-like plates. In the pure condition it

appears as six-sided plates, which are superposed in layers. The crystals possess a splendid silvery lustre, and are rather difficultly soluble in cold water; less so in hot water.

The AUROCHLORIDE, $C_4H_{12}N_2.2HCl.2AuCl_3 + 2H_2O$, crystallizes likewise in plates, which are difficultly soluble in cold water. It can, therefore, be readily separated from cadaverine aurochloride, which is easily soluble in water. The water of crystallization can be driven off completely only at 110° (BRIEGER). According to BOCKLISCH, it loses this water on standing over sulphuric acid, or on heating at 100°.

The PICRATE, $C_4H_{12}N_2.2C_6H_2(NO_2)_3OH$, is difficultly soluble, and crystallizes from a hot aqueous solution in needles; from hot aqueous alcohol on cooling in yellow plates. It begins to brown at 230°, and on further heating becomes darker, till finally, at 250°, it decomposes with rapid evolution of gas (BOCKLISCH).

The CARBONATE is crystalline.

The MERCURY DOUBLE SALT is easily soluble in a large quantity of water, and can thus be separated from the cadaverine salt, which is difficultly soluble. From hot concentrated aqueous solution it crystallizes in needles.

CADAVERINE, $C_5H_{14}N_2$, is a diamine isomeric with neuridine, and, like the latter, it occurs very frequently in decomposing animal tissues. It is a very striking fact, that in ordinary putrefaction as choline disappears the diamines appear and increase in quantity according as the time of putrefaction is extended. It has been obtained by BRIEGER from human lungs, hearts, livers, etc. (hence the name), which were allowed to putrefy at the ordinary temperature for three days; from the same organs, and from horseflesh, after four months in a closed vessel at — 9° to + 5°;

from putrid mussel after sixteen days; and it seems to be a constant product of the growth of the comma bacillus, irrespective of the soil on which it is cultivated.

BOCKLISCH has isolated it from perch and pike, six days in midsummer; from herring, twelve days in spring; from haddock, two months at a low temperature; from cultivations of FINKLER and PRIOR'S vibrio proteus on beef-broth, thirty to thirty-five days at 37° to 38° (*Ber.* **20**, 1441). Cadaverine seems to be a constant product of the activity of the genus vibrio, inasmuch as it does not occur in cultures in which this germ is absent. Thus, it is not present in the excrements of healthy or typhoid patients; in cultures of EMMERICH'S bacillus, typhus bacillus, and of the micrococci of pus. OECHSNER DE CONINCK has found it in putrid jelly-fish (HOGOUNENQ, page 23). Cadaverine occurs in the mercuric chloride precipitate, from which it is isolated according to the methods given on pages 155 and 169.

This base was at first ascribed the formula $C_5H_{16}N_2$, but subsequent researches led BRIEGER and BOCKLISCH to the adoption of the formula $C_5H_{14}N_2$. In 1883, LADENBURG prepared, as the first step in the synthesis of piperidine, a base, pentamethylenediamine, possessing the same empirical formula as cadaverine, and later (*Ber.* **18**, 2956) he showed the possibility of the identity of these two bases. This led to their direct comparison and the successful establishment of their identity. In fact, LADENBURG, as a crucial test of the identity, converted cadaverine into piperidine, and found the latter base to agree entirely in its chemical and physical properties with those of the natural alkaloid (*Ber.* **19**, 2586). LADENBURG, however, observed one apparent difference between cadaverine and pentamethylenediamine, and that was in the composition of the mercury double salts. That of the former base, whether obtained from alcoholic

or aqueous solution (BOCKLISCH, *Ber.* **20**, 1441), was found to combine with four molecules of mercuric chloride; whereas the double salt of pentamethylenediamine was found by LADENBURG to contain only three molecules of mercuric chloride. Subsequently he found that he had prepared this salt by mixing the aqueous solutions of the hydrochloride of the base and of the mercuric chloride in the molecular ratio of 1 to 4, and on using a larger excess of mercuric chloride he obtained a salt containing four molecules of mercuric chloride (*Ber.* **20**, 2216). The complete identity of these two bases has, therefore, been established. The constitutional formula of cadaverine is, therefore:

$$NH_2—CH_2—CH_2—CH_2—CH_2—CH_2—NH_2.$$

Cadaverine forms a somewhat thick, water-clear, syrupy liquid, which possesses an exceedingly unpleasant odor, resembling somewhat that of coniine (piperidine) and of semen. When dehydrated with potassium hydrate it boils at 115°–120° (BRIEGER). It boils at 175° (BRIEGER, III., 98), and fumes in the air. The base eagerly absorbs carbonic acid from the air, and solidifies into a crystalline mass. It is volatile with steam, and can be distilled, without decomposition, even in presence of sodium or barium hydrate, or soda lime. Neuridine, its isomer, decomposes under these circumstances. When heated with alcoholic potash and chloroform it does not give the iso-nitril reaction, nor does it give the characteristic odor of oil of mustard on treatment with carbon disulphide and mercuric chloride. These two reactions are given by primary monamines, but in this case they are not given by cadaverine, a primary diamine. It is probable that this behavior holds true for all diamines.

Cadaverine is, undoubtedly, identical with the so-called "animal coniine," which has been isolated at various times from cadavers.

Cadaverine and putrescine were at first regarded as physiologically indifferent, but more recent investigations by SCHEURLEN, GRAWITZ, and others, show that both these bases are capable of producing strong inflammation and necrosis. In cholera Asiatica the necrosis of the intestinal epithelium is quite common, and it would seem that this pathological change is due to the presence of these bases. Besides these local effects, they prevent, even in small quantity, the coagulation of blood, and render it "laky." According to GRAWITZ, cadaverine seems to hinder the growth of bacteria. Both bases are also optically inactive.

When cadaverine is treated with methyl iodide, there is obtained a base, the hydrochloride of which gives with platinum chloride a double salt, having the composition: $C_5H_{12}(CH_3)_2N_2.2HCl.PtCl_4$. This new base, therefore, is cadaverine, in which two atoms of hydrogen have been replaced by two methyl radicals. The platinochloride of this derivative forms long, clear red needles, which, unlike those of cadaverine, do not change their shape on repeated recrystallization. It is moderately difficultly soluble in water (BRIEGER, II., 41). Since cadaverine is a primary diamine it should combine with six molecules of methyl iodide to form a saturated compound. This, however, has not been obtained.

The HYDROCHLORIDE, $C_5H_{14}N_2.2HCl$, crystallizes in beautiful, long deliquescent needles (BRIEGER). According to BOCKLISCH, it forms long colorless needles or prisms; crystallizes from alcohol in plates and is not deliquescent. It is soluble in water, alcohol, alcohol-ether; but is insoluble in absolute alcohol, ether, etc. It can readily be separated

from putrescine hydrochloride by its solubility in 96 per cent. alcohol (BOCKLISCH). The strictly pure base, as well as the hydrochloride, does not give a blue color with ferric chloride and potassium ferricyanide. For reactions of the hydrochloride and of the free base, see Table I.

Cadaverine hydrochloride on dry distillation decomposes into NH_3, HCl, and piperidine, $C_5H_{11}N$. The latter is a well-known poisonous alkaloid which exists in the combined state in black pepper. It is not known whether this change, whereby the non-poisonous cadaverine is converted into a toxic base, can take place under the influence of bacteria during the processes of putrefaction or not. However, it does not seem improbable that this simple chemical change should be effected through the action of living organisms; for SCHMIDT has already shown that the almost physiologically indifferent choline, when subjected to the action of the bacteria of hay-infusion, decomposes into a neurine-like base possessing a muscarine-like action, and under certain conditions it yields a base which in its action resembles pilocarpine.

The SULPHATE likewise forms beautiful, well-formed needles, and in its solubility corresponds to the hydrochloride.

The PLATINOCHLORIDE, $C_5H_{14}N_2.2HCl.PtCl_4$ (Pt = 38.49 per cent.), crystallizes after some time, on the addition of platinum chloride to a not too concentrated solution of the hydrochloride, in the form of long, beautiful orange-red needles (BOCKLISCH). Ordinarily it is obtained at first in long, dirty red needles, which on repeated recrystallization become clearer, and assume a form similar to that of ammonium platinochloride. It forms chrome-yellow rhombic prisms which are short and octahedra-like. In polarized light they are strongly double refracting. It is very slightly

soluble in cold water; can be recrystallized from hot water (Bocklisch).

The Aurochloride, $C_5H_{14}N_2.2HCl.2AuCl_3$ (Au = 50.25 per cent.), crystallizes partly in cubes, and partly in long needles which at first possess a bright lustre, but under the desiccator soon effloresce and become opaque. The water of crystallization is completely removed on standing over sulphuric acid. It is very easily soluble, and melts at 188° (Bocklisch).

The Picrate, $C_5H_{14}N_2.2C_6H_2(NO_2)_3OH$, forms yellow plates which are difficultly soluble in cold water. From hot water it crystallizes in long prisms, which melt at 221° with decomposition. It is insoluble in absolute alcohol and can be recrystallized from hot dilute alcohol.

Cadaverine hydrochloride combines with mercuric chloride, when the aqueous solutions of these two salts are mixed in the molecular ratio of 1 to 4, to form $C_5H_{14}N_2.2HCl.3HgCl_2$. This salt can be recrystallized from hot water (Ladenburg). When an excess of mercuric chloride is used the double salt has the composition $C_5H_{14}N_2.2HCl.4HgCl_2$. This last salt melts at 216° (Ladenburg); at 214° (Bocklisch). It is difficultly soluble in cold water; from hot water it crystallizes in needles or plates (Bocklisch).

The Neutral Oxalate, $C_5H_{14}N_2.H_2C_2O_4 + 2H_2O$, was prepared by Bocklisch by adding a little less than the calculated quantity of alcoholic oxalic acid to the cadaverine. The precipitate may be recrystallized from hot dilute alcohol, when it is obtained in the form of needles, which melt at about 160° and at the same time give off gas.

The Acid Oxalate, $C_5H_{14}N_2.2H_2C_2O_4 + H_2O$, is made by bringing the neutral salt into alcoholic oxalic acid. It is soluble in hot dilute alcohol, and recrystallizes from it in

quadratic plates, sometimes in glistening needles. It melts at 143° with decomposition. After it has been dried over sulphuric acid, it loses on being heated to 105°–110° one molecule of water (BOCKLISCH, *Ber.* **20**, 1441). The insolubility of these oxalates in absolute alcohol shows the fallacy of TAMBA's distinction between ptomaines and vegetable alkaloids. (See page 124.)

NEURIDINE, $C_5H_{14}N_2$, was the first diamine isolated from animal tissues (BRIEGER, 1884). It is one of the most common products of putrefaction, and as such has been obtained by BRIEGER from putrid horseflesh, beef, human muscle, five to six days; from haddock, five days in summer; from cheese, six weeks in summer; from gelatine, ten days at 35°; from decomposing human internal organs, three to eleven days.

BOCKLISCH has obtained it from perch, six days in summer; from barbel after three days in summer.

It has also been obtained from fresh eggs in the preparation of choline by heating with baryta; and also from fresh brain by heating with two per cent. hydrochloric acid (BRIEGER, I., 57–61).

Neuridine is almost invariably accompanied by choline, and as the duration of putrefaction increases, the latter gradually decreases in amount and yields a corresponding increase in trimethylamine, whereas, the yield of neuridine increases from day to day. The amount of neuridine formed depends upon the nature of the organ employed in putrefaction. The greatest yield is obtained from gelatinous tissues, such as intestines; and especially from pure gelatine. On the other hand, such tissues as the spleen and liver yield but little.

Neuridine comes down in the mercuric chloride precipi-

tate (sometimes it occurs in the filtrate), and can then be isolated from the other bases present in a number of ways. One method is given on page 205. Another convenient method of separation is to precipitate it from alcoholic solution by alcoholic picric acid. The picrate thus obtained is, for the purpose of further purification, recrystallized from absolute alcohol, then decomposed by extracting its acid solution with ether (to remove the picric acid) and evaporating the aqueous solution to dryness. The residue is now extracted with alcohol and the alcoholic solution precipitated by alcoholic platinum chloride. The platinochloride can now be recrystallized from hot water.

The free base, as obtained by the treatment of the hydrochloride with moist freshly precipitated silver oxide, possesses an extremely repulsive odor, similar to that of human semen. On evaporation of its aqueous solution it yields a gelatinous-like mass, and at the same time slowly decomposes. It does not crystallize when evaporated in a vacuum, and decomposes even under these conditions. The same disagreeable odor is obtained when the hydrochloride is warmed with potassium hydrate. BRIEGER (I., 24) regards this decomposition-product of neuridine as an oxidation-product of the original substance.

The free base is very readily soluble in water, but is insoluble in ether and absolute alcohol; difficultly soluble in amyl alcohol. It gives white precipitates with mercuric chloride, neutral and basic lead acetates. When distilled with fixed alkali it yields di- and tri-methylamine, thus probably showing some relation to neurine, hence the name neuridine. It does not give HOFFMANN'S iso-nitril reaction, but it does not follow from this, as shown under cadaverine, that it may not be a primary diamine. It is isomeric with cadaverine.

The HYDROCHLORIDE, $C_5H_{14}N_2.2HCl$, crystallizes in long needles which are extremely soluble in water and in dilute alcohol, but are insoluble in absolute alcohol, ether, benzole, chloroform, petroleum ether, benzene, amyl alcohol, etc. Its insolubility in absolute alcohol may be used to effect a separation from choline hydrochloride. It can be recrystallized from slightly warm dilute alcohol. Although the pure salt is insoluble in the reagents just given, nevertheless, in the presence of other animal matter it is dissolved in greater or less quantity, and hence can be obtained by the STAS-OTTO as well as by the DRAGENDORFF method. The crystals resemble urea in form. On heating very cautiously the salt sublimes, and at the same time appears to undergo a partial internal decomposition, inasmuch as many of the groups of needles in the sublimate are colored red or blue. For the behavior of the hydrochloride with the alkaloidal reagents, see Table I.

Pure neuridine is not poisonous, but as long as it is contaminated with other putrefaction products it possesses a toxic action similar to that of peptotoxine. This holds true for the other non-poisonous bases.

The PLATINOCHLORIDE, $C_5H_{14}N_2.2HCl.PtCl_4$ (Pt= 38.49 per cent.), crystallizes in beautiful flat needles. Recrystallized from hot water, it forms aggregations of small, clear, yellow needles. It is readily soluble in water, from which it is precipitated on the addition of alcohol.

The AUROCHLORIDE, $C_5H_{14}N_2.2HCl.2AuCl_3$ (Au= 50.38 per cent.), is fairly difficultly soluble in cold water (BOCKLISCH), and crystallizes on cooling of the hot, saturated solution in bunches of clear, yellow, short needles.

The PICRATE, $C_5H_{14}N_2.2C_6H_2(NO_2)_3OH$, can be recrystallized from boiling water, in which it is very difficultly soluble, in the form of needles united in plumose groups. It is almost insoluble in cold water; less difficultly soluble

in alcohol. It is not fusible, but begins to brown and give off yellow vapors at 230°, and carbonizes completely at 250°.

SAPRINE, $C_5H_{16}N_2$, was found in human livers and spleens after three weeks' putrefaction (BRIEGER, II., 30, 46, 58). It occurs together with cadaverine, putrescine, and mydaleine in the mercuric chloride precipitate. To separate these bases, BRIEGER used the following process: The mercury salts were decomposed with hydrogen sulphide, the filtrate evaporated to dryness, and the residue then extracted with alcohol. The putrescine hydrochloride is insoluble in alcohol, and is thus removed. The alcoholic solution was treated with platinum chloride, which precipitated the greater part of the cadaverine. The mother liquor, on concentration, yielded a mixture of the platinochlorides of cadaverine and saprine. Each successive crop contained more of the saprine double salt. The two kinds of crystals were now separated by means of a magnifying glass. The saprine platinochloride thus obtained was finally purified by repeated recrystallization from water. The mother liquor, after the removal of the saprine platinochloride, contains the mydaleine salt, which, on account of its solubility in water, crystallizes only on concentration, or on standing under a desiccator. The mercuric chloride filtrate contains some mydaleine and the ptomaine which yields a platinochloride containing 28.40 per cent. platinum.

The free base is a diamine. It possesses a weak pyridine-like odor, and can be distilled with steam or with potassium hydrate without undergoing decomposition. In its reactions it behaves the same as cadaverine, except that it gives an amorphous precipitate with potassium-bismuth iodide, whereas cadaverine gives a crystalline precipitate.

The free base gives an immediate intense blue color with ferric chloride and potassium ferricyanide.

The HYDROCHLORIDE, $C_5H_{16}N_2.2HCl$, forms flat needles which are not hygroscopic (distinction from cadaverine hydrochloride). Its reactions are the same as those of cadaverine hydrochloride (see Table I.). It is, however, tinged slightly blue by a mixture of ferric chloride and potassium ferricyanide, whereas the free base gives an intense blue. It differs from cadaverine in that it does not give the reddish-brown color with potassium bichromate and sulphuric acid. Again, it forms no aurochloride; while, on the other hand, cadaverine hydrochloride yields an easily soluble salt, crystallizing in splendid needles.

The PLATINOCHLORIDE, $C_5H_{16}N_2.2HCl.PtCl_4$, forms parallel, aggregated, pointed crystals, which are somewhat soluble in water, and are thus distinguished from cadaverine platinochloride, which crystallizes in rhombs, and is difficultly soluble in water. Saprine does not form an aurochloride. Physiologically, it is indifferent.

A BASE, $C_7H_{10}N_2$.—Until very recently the nature of the basic substances which are formed as products of the alcoholic fermentation of sugar or molasses has been but little understood. KRÄMER and PINNER, in 1869, found in crude fusel oil a small quantity of a volatile base which they apparently identified with a collidine. This observation was confirmed by ORDONNEAU, and others; and still more recently (January, 1888) MORIN has contributed an elaborate paper upon the bases formed during alcoholic fermentation. The portion of crude fusel oil which boils above 130.5° was extracted with slightly acidulated water, the acid aqueous solution thus obtained was made alkaline, and the oily bases which were thus set free were then distilled with

vapor of water. The free bases were dried over potassium hydrate and then subjected to fractional distillation. Three fractions were thus obtained, boiling respectively at 155°–160°, 171°–172°, and 185°–190°. Only the second fraction, which boils at 171°–172°, was studied and was found to possess the formula $C_7H_{10}N_2$. Heated with concentrated hydrochloric acid, it is decomposed in part with the formation of ammonia. It combines with ethyl iodide to form a yellow, crystalline compound, which is soluble in water and alcohol, insoluble in ether. The hydrochloride crystallizes in fine white needles, soluble in water and alcohol, and but very slightly soluble in absolute ether. The free base, as stated above, boils at 171°–172°, is very soluble in water, alcohol, ether, etc. When pure it forms a colorless, strongly refracting, very mobile oil, which possesses a characteristic nauseating odor, but slightly resembling that of the pyridine bases. Its density at 12° is 0.9826; toward litmus paper the base shows no decided reaction. The platinochloride is crystalline and is very soluble in water and alcohol, slightly soluble in ether. Potassio-mercuric iodide does not precipitate the aqueous solution of the free base, but in solutions of the hydrochloride it gives a yellow flocculent precipitate, which soon crystallizes in long brilliant yellow needles. This reaction takes place readily in solutions of 1 to 1000, and only after some hours in solutions of 1 to 10,000; and is not given by the bases of the pyridic and quinolinic series. Mercuric chloride produces an immediate flocculent precipitate in solutions of the base having a concentration of 1 to 1000; but requires some time to appear in 1 to 10,000. Phosphotungstic acid gives an immediate white precipitate even in a dilution of 1 to 10,000. Phosphomolybdic acid in solutions of the same strength yields a yellow precipitate.

The physiological action of this base has been examined by R. WURTZ, who found the lethal dose for rabbits, etc., to be about one gram per kilogram of body weight. It produces stupor, paralysis, which at first appears in the rear extremities; the sensibility becomes diminished and the pupils are dilated and unresponsive to light; the rate of heart beat is lowered, and the rectal temperature falls as low as 35°; death follows a more or less prolonged coma.

TANRET obtained by the action of ammonia on glucose a number of bases to which he applied the generic name of glucosines. One of these, having the formula $C_{14}H_{10}N_2$ (C = 6), corresponds in its formula and its general properties to MORIN'S base $C_7H_{10}N_2$ (C = 12), and, in fact, the two bases are considered by TANRET to be identical.

It is interesting to note in this connection that alkaloidal bases have been found in petroleum by BANDROWSKI, and that similar basic substances have been detected by WELLER in paraffine oil.

Most of the solvents in common use, such as alcohol, ether, chloroform, benzole, petroleum ether, amyl alcohol, etc., have been shown at different times to contain basic pyridine compounds, though ordinarily in very minute quantity. On the other hand, HAITINGER has found in some specimens of amyl alcohol as much as 0.5 per cent. of pyridine.

METHYL-GUANIDINE, $C_2H_7N_3 = NH{=}C\begin{matrix}NH{-}CH_3\\NH_2\end{matrix}$. —This base has long been known as a product of the oxidation of creatine and creatinine, but had never been met with in animal tissues. BRIEGER (III., 33) has obtained it from horseflesh which was allowed to decompose in a closed vessel at a low temperature (— 9° to + 5°) for four months. BOCKLISCH (*Ber.* **20**, 1441) has obtained it from impure

cultures on beef-broth of FINKLER and PRIOR'S vibrio proteus, containing ordinary putrefaction bacteria, for twenty to thirty days at 37°–38°. Vibrio proteus alone seems incapable of forming this base. The comma bacillus after some time (six weeks) partially decomposes creatinine with formation of a small quantity of methyl-guanidine.

It occurs in the mercuric chloride filtrate (BRIEGER), from which it is obtained, after the removal of the mercury by hydrogen sulphide, by precipitation with phosphomolybdic acid. The precipitate is decomposed with neutral lead acetate, and the filtrate from this, after removal of the lead by hydrogen sulphide, is concentrated and then sodium picrate added. The resinous picrate precipitate is purified by boiling with much water, and, finally, it is recrystallized from boiling absolute alcohol. According to BOCKLISCH, it occurs in the mercuric chloride precipitate (not in the filtrate), from which it is isolated, after removal of the mercury and concentration of the clear filtrate, by precipitation with sodium picrate. The precipitate containing cadaverine, methyl-guanidine, and creatinine, is boiled with absolute alcohol (cadaverine picrate is insoluble) and the alcoholic solution is then evaporated to drive off alcohol and taken up with water. From this aqueous solution, after removal of picric acid, methyl-guanidine is precipitated by gold chloride, whereas creatinine remains in solution.

This ptomaine is identical with the synthetic methyl-guanidine (methyluramine) which can be readily obtained by boiling a creatine solution with mercuric oxide or with lead dioxide and dilute sulphuric acid (DESSAIGNES). The parent substance of methyl-guanidine as it occurs in putrefaction is undoubtedly the creatine which exists preformed in the muscular tissue. If such is the case, the bacteria engaged

in its production must be considered as possessing an oxidizing action, since this base is prepared synthetically from creatine by oxidation. That creatine does not offer much resistance to the action of bacteria is shown in the fact that FRIEDLÄNDER'S pneumonia coccus, which possesses but small chemical powers, is capable of slowly but steadily decomposing creatine, yielding as one of the products acetic acid. STRECKER and ERLENMEYER, as well as BAUMANN, have shown that creatine, although a substituted guanidine, is not poisonous, but it is readily converted into creatinine, which is a relatively toxic substance. On the other hand, guanidine and methyl-guanidine are quite violent poisons. This is, therefore, another instance in which a toxic substance is formed by the action of bacteria from a previously non-poisonous base (see page 190). According to LOSSEN, guanidine is formed, although in small quantity, in the oxidation of albumin.

The formulæ of these closely related substances are here given for comparison :

Creatine, $NH=C\begin{cases}N(CH_3).CH_2.CO_2H\\NH_2\end{cases}$

Creatinine, $NH=C\begin{cases}N(CH_3).CH_2\\NH-CO\end{cases}$

Methyl-guanidine, $NH=C\begin{cases}NH.CH_3\\NH_2\end{cases}$

Guanidine, $NH=C\begin{cases}NH_2\\NH_2\end{cases}$.

METHYL-GUANIDINE forms a colorless, easily deliquescent mass possessing a strong alkaline reaction. On heating with potassium hydrate it decomposes, and yields ammonia and methylamine. It is a highly poisonous base.

The HYDROCHLORIDE, $C_2H_7N_3.HCl$, can be obtained from the picrate by dissolving the latter in water acidulated with hydrochloric acid, and extracting the solution with ether to remove the picric acid. The colorless aqueous solution now, on evaporation, yields a thin syrup which crystallizes in vacuum to compact prisms. These are insoluble in alcohol, and give with platinum chloride a double salt of monoclinic needles (HAUSHOFER) which are very easily soluble (1 part in about 7 parts water, TATARINOW).

The AUROCHLORIDE, $C_2H_7N_3.HCl.AuCl_3$ (Au = 47.70 per cent.), forms rhombic crystals (HAUSHOFER) which are easily soluble in ether, more difficultly in water or alcohol. It readily decomposes on heating in pure water, but may be recrystallized from water acidulated with hydrochloric acid. It melts at 198°.

The PICRATE, $C_2H_7N_3.C_6H_2(NO_2)_3OH$, comes down at first as a resinous precipitate, which when boiled with much water solidifies in the form of felted needles. It is very difficultly soluble in water, and can be purified by repeated recrystallization from boiling absolute alcohol—distinction from cadaverine. It melts at 192°.

The OXALATE, $(C_2H_7N_3)_2.H_2C_2O_4+2H_2O$, forms crystals which are easily soluble in water.

PHYSIOLOGICAL ACTION.—Methyl-guanidine as obtained from putrefying flesh is identical in its physiological action with the synthetic base. It has already been stated that the non-poisonous creatine is readily converted into the relatively energetic poison creatinine. The latter substance possesses a paralyzing action differing very much from its decomposition-product methyl-guanidine. This base is very poisonous, and the symptoms are marked by dyspnœa, muscle tremor, and general clonic convulsions. BRIEGER has observed the following symptoms on injection of about

0.2 gram of methyl-guanidine into a guinea-pig. The respiration at once becomes more rapid, and in a few minutes abundant passage of urine and stool takes place; the pupils dilate rapidly to the maximum and cease to react. The animal is uneasy but motionless, though not exactly paralyzed. Respiration becomes deeper and more labored, the head moves from side to side, the extremities become gradually paralyzed; dyspnœa sets in, the animal falls on its side and dies (twenty minutes) amid general clonic convulsions of short duration. Fibrillary twitchings of the trunk muscles are observed only in the beginning. Post-mortem showed the heart to be stopped in diastole, the intestines filled with fluid, the bladder contracted, the cortex of the kidney hyperæmic, but the papillæ of the kidneys surprisingly pale.

A BASE, $C_{13}N_{20}N_4$, was obtained as early as 1868 by OSER, who observed its formation during the fermentation of pure cane-sugar by means of yeast. The hydrochloride when dried in vacuo is said to form a white, very hygroscopic foliaceous mass, which soon becomes brown on exposure to air. At first it imparts a burning taste, which is soon replaced by a very bitter sensation.

A BASE corresponding to the formula $C_{17}H_{38}N_4$ was obtained by GAUTIER and ETARD from the mother liquors of the platinochloride of the base $C_8H_{13}N$. Very little is known, however, in regard to the general properties of this base, owing to the small quantity which could be isolated. This base and the one obtained by OSER from the yeast fermentation of sugar, $C_{13}H_{20}N_4$, are the only ptomaines thus far isolated which are known to contain four atoms of nitrogen.

The PLATINOCHLORIDE, $C_{17}H_{38}N_4.2HCl.PtCl_4$ (Pt = 27.55 per cent.), is readily soluble, and crystallizes in needles which possess a light yellow flesh color. When heated to 100°, it slowly decomposes, giving off a seringa-like odor.

MYDINE, $C_8H_{11}NO$, is a non-poisonous base which has been obtained by BRIEGER (III., 25) from the putrefaction of about two hundred pounds of human internal organs. It occurs in the mercuric chloride filtrate, and is isolated from it after the removal of the mercury by hydrogen sulphide, by precipitation with phosphomolybdic acid. The gummy precipitate which is produced is decomposed on the water-bath with a solution of neutral lead acetate, and the filtrate on evaporation yields a colorless hydrochloride, crystallizing in plates. It is purified by recrystallization of the picrate.

The free base is strongly alkaline, and possesses an ammoniacal odor. It is characterized by its strong reducing properties. The name mydine is derived from μυδάω, to putrefy. With platinum chloride it gives, after a time, an extremely soluble salt; with gold chloride, a precipitate of metallic gold. On distillation it is decomposed.

The HYDROCHLORIDE, $C_8H_{11}NO.HCl$, crystallizes in colorless plates. It gives a blue color with ferric chloride and potassium ferricyanide.

The PICRATE, $C_8H_{11}NO.C_6H_2(NO_2)_3OH$, is obtained in broad prisms, which melt at 195°. It is the only salt suitable for manipulations.

In describing NENCKI's collidine (page 149) it was stated that tyrosin might be looked upon as the source of that base. It would seem, however, to be more appropriately the parent substance of mydine, inasmuch as it decomposes

on being heated to 270° into carbonic acid and oxyphenyl-ethylamine, $C_8H_{11}NO$. The change that takes place can be represented by the equation:

$$C_6H_4\begin{matrix}OH\\ \diagdown CH_2.CHNH_2.CO_2H\end{matrix} = C_6H_4\begin{matrix}OH\\ \diagdown CH_2.CH_2NH_2\end{matrix} + CO_2.$$

Tyrosin. Oxyphenyl-ethylamine.

A Base, $C_5H_{11}NO_2$, was isolated by E. and H. Salkowski (1883) from decomposing fibrin and meat. In its composition it is isomeric with betaine anhydride. It is extremely soluble in water, very difficultly so in alcohol, insoluble in ether, and possesses a semen-like odor and saline taste. The aqueous solution, which is not alkaline in reaction, yields on evaporation a stellate crystalline mass, which on standing over sulphuric acid becomes a white powder, which melts at 156°. It dissolves silver oxide, but not cupric hydrate, thus showing that it is not an amido acid. Moreover, it does not give a precipitate or blue coloration with copper acetate, or ammoniacal silver nitrate. The base does not seem to possess a toxic action.

The Hydrochloride, $C_5H_{11}NO_2.HCl$, forms colorless, stellate crystals, which are permanent in the air, and are extremely soluble in water, even in absolute alcohol.

The Aurochloride, $C_5H_{11}NO_2.HCl.AuCl_3+H_2O$, is obtained on slow evaporation, as large, well-formed, beautiful dark yellow crystals. They are probably monoclinic, contain water of crystallization, and melt at below 100°.

The Platinochloride gave on analysis results corresponding to the formula $(C_7H_{15}NO_2.HCl)_2PtCl_4$. This may possibly be due to the presence of some higher homologues of the base $C_5H_{11}NO_2$. It forms fine orange-yellow crystals, which are very difficultly soluble in alcohol, easily

so in hot water, from which, on cooling, it crystallizes in beautiful plates.

CHOLINE GROUP.—The following four bases are closely related, and, indeed, starting from choline, the oldest and best known individual, the remaining bases can be readily prepared from it. Moreover, they can all be prepared synthetically according to methods that will be subsequently indicated. As choline is the most prominent member, we have thought best to class these substances together as constituting the choline group. It is very probable that mydatoxine and mytilotoxine, when their constitution becomes known, will be found to be homologues of certain members of this group.

NEURINE, $C_5H_{13}NO = C_2H_3.N(CH_3)_3.OH$.—This substance was obtained and named thus by LIEBREICH (1865), who prepared it by boiling protagon for twenty-four hours with concentrated baryta. Previous to its discovery as a decomposition-product of protagon from the brain it was prepared synthetically by HOFFMANN (1858) by treating trimethylamine and ethylene bromide with potassium hydrate or silver oxide. BAEYER (1866), by boiling an alcoholic extract of the brain with baryta water, obtained on separation by three different methods, a base, or rather a mixture of bases, which, on analysis, gave results corresponding to the three formulæ:

1.	2.	3.
$(C_5H_{14}NOCl)_2PtCl_4$	$(C_5H_{12}NCl)_2PtCl_4$	$(C_5H_{14}NCl)_2PtCl_4$

Formula No. 3 was the one accepted by LIEBREICH for neurine, but, according to BAEYER, LIEBREICH'S neurine salt is not simple, but is a mixture of Nos. 1 and 2. He,

himself, accepts formula No. 1 as the platinochloride of neurine, and distinctly states (*Annal. d. Chem. u. Pharm.*, **142**, 323, 1867) that neurine is in composition trimethyloxyethyl-ammonium hydroxide. And, according to him, choline from bile, and sinkaline from white mustard, appear to be identical with neurine.

This nomenclature of BAEYER'S was at first adopted by WURTZ and others, who showed that the oxyethyl base was identical with choline and sinkaline. On that account STRECKER, in 1868 (*Annal.*, **148**, 79), suggested the restriction of the name choline to the oxyethyl base, and to reserve the name neurine for the base whose platinochloride is represented in No. 3, as originally was done by LIEBREICH. In 1869 LIEBREICH showed conclusively that pure protagon, when heated with baryta for twenty-four hours, yields a substance having the composition of the vinyl base:

$$N(CH_3)_3.C_2H_3.OH.$$

The platinochloride of this base crystallized in five-sided yellow plates, which, after a time, on exposure to the air, became cloudy; on treatment now with water a portion dissolved, and the solution was found to contain the oxyethyl base. Furthermore, he observed that when the alcoholic extract of the brain, from which all the protagon had been removed, is treated with baryta, only the latter, the oxyethyl base, is obtained. Finally, in 1870, WURTZ abandoned the use of the term neurine to designate the oxyethyl base, and returned to the name choline, originally applied to the oxyethyl base by its discoverer, STRECKER. Nevertheless, the confusion in the use of these two terms continued to exist, and even at the present time it is the cause of no little misunderstanding. Thus, MARINO-ZUCO

(1885), in his excellent researches on the genesis of ptomaines, applies the term neurine, following BAEYER'S precedent, to the oxyethyl base, $C_5H_{15}NO_2$, which is really choline, according to the proper nomenclature.

We have gone somewhat at this point in detail into the history and the proper use of the terms neurine and choline because of the confusion which is sure to arise if the distinction is not thoroughly borne in mind. The name neurine, then, should be used only to denote the vinyl base $C_5H_{13}NO$. It is trimethyl-vinyl-ammonium hydrate. On the other hand, choline is applied to the oxyethyl base $C_5H_{15}NO_2$, which is trimethyl-oxyethyl-ammonium hydrate.

Neurine has been obtained by BRIEGER in the putrefaction of horse, beef, and human flesh for five to six days in summer. It also occurs in the commercial, so-called "neurine," together with choline (BRIEGER, I., 34). LIEBREICH obtained it in the decomposition of protagon by baryta. And BRIEGER (I., 60) also has isolated it along with choline from fresh human brains, by boiling with baryta; but has not obtained it by digesting the brains on the water-bath with two per cent. hydrochloric acid.

The genesis of neurine is still rather obscure, and it is to be hoped that future investigations may shed more light upon the mysterious production of this highly poisonous base. Its occurrence in the brain together with choline would seem to indicate that it is either derived from choline by the removal of water, or that it exists together with choline, partly replacing the latter in the molecule of protagon (lecithin), according to the hypothesis put forward by LIPPMANN (page 188). The question of its derivation from choline by withdrawal of a molecule of water has already been subjected to an interesting experimental discussion. CH. GRAM attempted to explain the production of neurine

and other muscarine-like ptomaines as due to the dehydrating action of the acids employed in the methods of extraction, and, indeed, he claimed to have converted choline platinochloride, by heating with hydrochloric acid, into neurine. This statement has been disputed by BRIEGER, who showed that the platinochloride of choline, as well as the hydrochloride, may be heated with fifteen or thirty per cent., or even concentrated hydrochloric acid, for six to eight hours on a water-bath, without any conversion whatever (III., 15). That neurine may be obtained from choline, at least by chemical processes, was shown by BAEYER, in 1866, who found that choline chloride, when heated with several times its volume of concentrated hydriodic acid and some red phosphorus, gave a compound $C_5H_{13}NI_2$, which, on digestion with fresh, moist silver oxide, yielded a vinyl base identical with that previously obtained synthetically by HOFFMANN, and now known as neurine. BRIEGER has tried, unsuccessfully, to bring about this dehydration by the putrefaction of pure choline (I., 59). However, SCHMIDT and WEISS (1887) were more successful, and they found that choline, as well as the hydrochloride and lactate, is changed by the action of microörganisms into the strongly poisonous neurine. Their results are given in full under choline (see page 190).

Neurine is almost invariably accompanied by choline, from which, however, it can be readily separated by the difference in the solubilities of the platinochlorides. It occurs in the mercuric chloride precipitate (and in the filtrate), and from this it can be obtained, after removal of the mercury, by precipitating the solution of the mixed hydrochlorides in absolute alcohol by platinum chloride. The platinochlorides are then separated by recrystallization

from water, since the neurine is difficultly soluble, whilst the choline salt is readily soluble.

The free base possesses a strong alkaline reaction, and on contact with the fumes of hydrochloric acid it yields a cloud. According to LIEBREICH, the alkaline solution cannot be neutralized by passing through it carbonic acid.

The CHLORIDE, $C_5H_{12}N.Cl$, is extremely poisonous, and crystallizes in fine hygroscopic needles.

The PLATINOCHLORIDE, $(C_5H_{12}N.Cl)_2PtCl_4$ (Pt=33.96 per cent.), is difficultly soluble in hot water, and crystallizes in beautiful, well-formed octahedra belonging to the regular system. No twin-crystals are observed. Sometimes the crystals contain water of crystallization, at other times they do not (BRIEGER, I., 33). According to LIEBREICH, it forms from an aqueous solution in five- or six-sided, heaped-up plates resembling urea nitrate, whilst from an alcoholic solution it forms needles, which on exposure to air become opaque, and are partially converted into the oxyethyl base —choline.

The AUROCHLORIDE, $C_5H_{12}N.Cl.AuCl_3$ (Au=46.35 per cent.), forms flat prisms, which are difficultly soluble in hot water (BRIEGER). Dissolves easily, and can be purified by crystallization (LIEBREICH).

PHYSIOLOGICAL ACTION.—Neurine is exceedingly poisonous, even in small doses, and in its action it strongly partakes of the characteristic stamp of poisoning by muscarine. The injection of a few milligrams into frogs produces in a short time a complete paralysis of the extremities, with deadening of reflex excitability. Respiration stops first, whilst the rate of heart-beat gradually decreases till, finally, a stoppage in diastole takes place. The injection of atropine at this point does away with the effect of neurine, so that the heart begins to beat again. Previously atropinized

frogs, as a rule, withstand the action of the poison. Immediately after the introduction of this substance there can be observed a distinct period of exaltation, which, however, soon gives way to the characteristic stage of depression, seen in the progressive slowing of the rate of heart-beat. Of the warm-blooded animals, cats seem to be much more sensitive to its action than mice, rabbits, or guinea-pigs. The symptoms seen in rabbits are profuse moistening of the nasal cavities and upper lip, which is succeeded by an intensely profuse salivation; later on there is noticeable an abundant secretion from the nasal mucous membrane and from the eyes; the latter, however, ceases in a short time. The movements of the heart and of respiration are at first quickened and strengthened, but before long the paralytic effects produce a constant slowing and weakening, till finally complete cessation of both movements results. The decided dyspnœa observed gradually alters its character, and just before death the respiration is irregular and superficial. The heart, as in frogs, continues to beat after the respiratory movements have ceased, till finally it stops in diastole. Direct application of concentrated solutions of the poison to the eyes produces almost always a contraction of the pupil, whilst a similar but less constant contraction is seen when it is injected. The peristaltic action of the intestines is heightened to such an extent that continual evacuation takes place. Just before death, violent clonic convulsions occur. Atropine possesses a strong antagonistic action toward neurine, and the injection of even a small quantity is sufficient to dispel the symptoms just described.

CHOLINE, $C_5H_{15}NO_2 = C_2H_4OH.N(CH_3)_3.OH$.—This base is identical with the sinkaline of VON BABO, the bilineurine of LIEBREICH, and the neurine of BAEYER,

MARINO-ZUCO, and others. According to SCHMIEDEBERG and HARNACK, it is identical with LETELLIER'S amanitine (agaricine), to which they assign, however, the formula $(CH_3)_3N.(CHOH.CH_3)OH$. Choline was first prepared, and so named, by STRECKER, in 1862, by treating hog-bile with hydrochloric acid. It was prepared synthetically by WURTZ (1868) by direct union of ethylene chlorhydrine and trimethylamine. The reaction that takes place can be represented by the equation :

$$C_2H_4\begin{cases} OH \\ Cl \end{cases} + \begin{matrix} CH_3 \\ CH_3 \\ CH_3 \end{matrix}\Big\} N = \begin{matrix} CH_3 \\ CH_3 \\ CH_3 \\ C_2H_4.OH \end{matrix}\Big\} NCl.$$

BAEYER (1866) obtained it by boiling an alcoholic extract of the brain with baryta water; and LIEBREICH, in 1869, showed that if the alcoholic extract, from which all the protagon had been removed, be thus treated, only choline is formed, whereas pure protagon, on heating with baryta, yields neurine. It has been obtained from the yolk of eggs; from bile; from fresh brains (BRIEGER); from fresh eggs, blood, lungs, and hearts, and lecithin (MARINO-ZUCO); from human placenta (BOEHM); from commercial neurine (BRIEGER); from fresh as well as decomposing internal organs of the cadaver (BRIEGER); from herring-brine and decomposing pike, three days in midsummer (BOCKLISCH). It has also been isolated from cultures of vibrio proteus (BOCKLISCH), and of comma bacillus (BRIEGER).

Not only has choline been met with in the animal tissues, but it has also been observed within the last few years to be very widely distributed in the vegetable kingdom. Thus, it has been found (HARNACK, 1876) accompanying muscarine, in toad-stool (Agaricus muscarius); in hops,

and hence in beer (GRIESS, HARROW); in the seeds of Trigonella (JAHNS); of white mustard as a glycoside (VON BABO); in ergot (BRIEGER); in the germs of pumpkins and lupines (SCHULZE, *Zeitschr. f. Physiol. Chem.*, **11**, 365); in Indian hemp (JAHNS); in beech-nuts and morels (Helvella esculenta, BÖHM); in Flores Sambuci, and extracts of belladonna and hyoscyamus (KUNZ), and Scopolia Japonica (SCHMIDT and HENSCHKE). According to LIPPMANN (*Ber.* **20**, 3206), it is present, together with betaine, in the molasses from beet-root sugar. Choline (RITTHAUSEN) and betaine (BÖHM) exist together in cotton-seeds; hence choline occurs in the press-cakes from cotton-seeds (BÖHM).

Choline may readily be prepared, after the method of DIAKONOW, from the yolk of eggs. These are extracted with ether, then with alcohol, and the extracts thus obtained are evaporated, and the resulting residues are boiled with baryta for one hour. The filtrate, after the removal of the barium by carbonic acid, is evaporated and the residue is extracted with absolute alcohol. The alcoholic solution is now precipitated with platinum chloride. BRIEGER (II., 55) has presented a method which is much simpler in its details and obviates the use of the expensive platinum chloride. The tissues rich in lecithin, as yolk of egg, brain, etc., are heated with concentrated hydrochloric acid for some hours on the water-bath. The insoluble residue is filtered off, and the filtrate, after neutralization of the excess of free acid with carbonate of sodium, is evaporated. The residue is extracted with alcohol, and the alcoholic solution is precipitated with alcoholic mercuric chloride. The precipitate thus obtained, on recrystallization several times from a large quantity of boiling water, yields the pure double salt of choline.

In regard to the genesis of choline the preponderance of

testimony goes to show that it is derived from the decomposition of lecithin, which, according to the researches of DIAKONOW and others, is one of the most widely distributed compounds, occurring in greater or less quantity in all of the animal tissues. Lecithin, which is a complex esther, decomposes under the action of acids and alkalies into a base (choline), glycerine, phosphoric acid, and fatty acids (stearic, oleic, palmitic, etc.). This change, which is readily brought about in the laboratory, is undoubtedly accomplished in a similar manner through the agency of bacteria. BRIEGER (II., 17) is inclined to believe that choline exists preformed in the various tissues, inasmuch as he has been unable to obtain it from the brain, which is rich in lecithin, by boiling with two per cent. hydrochloric acid. Prolonged heating with concentrated hydrochloric acid was necessary in order to obtain any choline from the brain. This result of BRIEGER'S is somewhat at variance with that of MARINO-ZUCO (see *Relazione*, etc., pages 29, 30, and 38), who obtained from 25 grams of lecithin, by the method of STAS, a small quantity of the aurochloride of a base, whilst from a similar amount he obtained more relevant quantities by the method of DRAGENDORFF.

The occurrence of choline in the vegetable kingdom would be unexplainable to us at present were it not that we now know of the existence of lecithin-like bodies in plants, from the decomposition of which substantially the same products are obtained as from the lecithin obtained from the animal tissues. The existence of such a body in plants was first predicted by SCHEIBLER in 1870, who was led to this conclusion in his celebrated study of beet-root sugar, because of the presence of oleic acid, glycerine, phosphoric acid, and betaine, as well as cholesterine, in the beet-root extracts. This hypothesis was confirmed by HOPPE-

SEYLER, who, in 1879, found a lecithin substance in yeast. SCHULZE found a similar compound in the cotyledons of lupine, whilst JACOBSON observed its presence in mustard-seeds, in fenugreek-seeds, in maize and wheat, in the fat from beans, peas, vetch, and lupines. HECKEL showed its presence in globularia, and LIPPMANN has found it in beet-root. According to HOPPE-SEYLER, this lecithin-like substance exists in all vegetable cells undergoing development. Up to the present time lecithin has always been supposed to contain a radical, which gives rise to choline on saponification, as an essential component, whilst on the other hand the fatty acids entering its molecule are well known to be replaceable by one another. Thus we may have a di-stearine lecithin as well as a di-oleine lecithin. Recent observations of LIPPMANN (*Ber.* **20**, 3206) show that the above basic radical, hitherto regarded as constant in lecithin, may possibly be capable of replacement by other similar radicals. He found on saponifying with baryta two different specimens of lecithin, both obtained from beet-root, that whilst one of them yielded oleic acid, glycerine, phosphoric acid, and betaine; the other lecithin gave oleic acid (and some other fatty acids), glycerine, phosphoric acid, and choline, with no betaine—at least not in isolable quantity. This remarkable difference has led LIPPMANN to suggest an explanation which, while it may not be the correct one, nevertheless possesses a high degree of probability. According to him, the lecithin molecule may contain interchangeable basic radicals in the same manner that it contains interchangeable acid radicals. This view is supported not only in the case of beet-root, where choline and betaine exist together, but the same two bases have been observed in cotton-seeds. A similar coexistence was observed in the toad-stool (Agaricus muscarius), in which choline and mus-

carine were found. And, lastly, the same condition holds true probably for mytilotoxine and betaine, which were shown to be present together in poisonous mussel.

Lecithin cannot always be regarded as the source of choline in plants, since this base is known to occur as a glucoside in the seeds of white mustard. The sinapin decomposes according to the equation:

$$\underset{\text{Sinapin.}}{C_{16}H_{23}NO_5} + 2H_2O = \underset{\text{Choline}}{C_5H_{15}NO_2} + \underset{\text{Sinapic Acid.}}{C_{11}H_{12}O_5}.$$

Decompositions of Choline.—Baeyer (1866) succeeded in converting choline into neurine by a purely chemical process. This was accomplished by heating choline chloride with concentrated hydriodic acid and red phosphorus in a sealed tube at 120°–150°, whereby the compound $C_5H_{13}NI_2$ was formed. The iod-iodide of choline thus obtained, on treatment with moist silver oxide gave a base whose platinochloride corresponded to the formula $(C_5H_{12}NCl)_2PtCl_4 + H_2O$. This double salt, according to Baeyer, is readily soluble in water, and gives reactions similar to choline. Although Baeyer is emphatic in his assertion that this is the vinyl compound (neurine) formed from the oxy-ethyl base (choline), yet it seems that there is room for doubt in regard to the interpretation of his results. Thus neurine platinochloride is difficultly soluble in water, contrary to the behavior of the platinochloride obtained by him. On the other hand, choline platinochloride is easily soluble in water, and it would seem, therefore, that Baeyer has not converted choline into neurine, but rather has regenerated choline from its iod-iodide. If such were the case, we would expect that the iod-iodide of neurine, $C_5H_{13}NI_2$, which has the same composition as the corresponding derivative of

choline, would yield, on treatment with silver oxide, the oxy-ethyl base. BAEYER has apparently not been able to effect this change, since he holds that the vinyl base may be prepared from the oxy-ethyl, but that the reverse, the preparation of the oxy-ethyl base from the vinyl compound, cannot be accomplished.

Whether the change described by BAEYER takes place or not, it is, nevertheless, certain that choline does not readily give up a molecule of water and thus become converted into neurine. CH. GRAM announced, in 1886, that choline chloride and lactate on heating on the water-bath decompose, and that this conversion into the vinyl base was complete when the aqueous hydrochloric acid solution of choline platinochloride was heated for five or six hours on the water-bath. In this way GRAM endeavored to explain the formation as due to the action of acids upon choline, but BRIEGER has shown that the platinum salt of choline, as well as its hydrochloride, can be heated with fifteen or thirty per cent., or even concentrated hydrochloric acid for six or eight hours without undergoing any change into neurine, thus disproving the results obtained by GRAM. E. SCHMIDT has confirmed BRIEGER'S observations in regard to the resistance of choline to decomposition by acids, but he has gone further, and has shown that what the action of acids has failed to do is readily accomplished through the agency of bacteria. He found that choline chloride, when allowed to stand with hay infusion, or with dilute blood for fourteen days at 30°–35°, is almost entirely decomposed yielding large quantities of trimethylamine and a base whose platinochloride resembles in form and solubility the double salt of neurine, and possesses a similar physiological action. Choline lactate in hay infusion developed an odor of trimethylamine in twelve hours,

but at the end of fourteen days a good deal of choline was still present. In this case no neurine was present, but instead a homologous base was found, which can be obtained synthetically by the action of trimethylamine on allyl bromide. According to MEYER, of Marburg, this base does not possess the muscarine-like action of neurine, but resembles more closely pilocarpine.

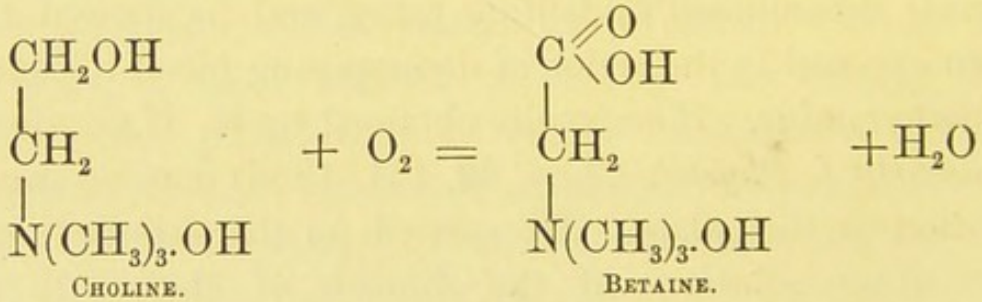
BRIEGER (I., 59) had unsuccessfully tried to transform choline into neurine by putrefaction. He observed that the choline decomposed with extreme slowness, even when the putrefaction was carried on at a higher temperature, yielding only trimethylamine. WURTZ (1868) showed that dilute solutions of free choline can be heated to boiling without any perceptible decomposition. Concentrated solutions, however, decompose with the formation of trimethylamine and glycol, $C_2H_4(OH)_2$. The decomposition of choline was studied somewhat by MAUTHNER (1873), who confirmed WURTZ'S observation that choline was scarcely decomposed by boiling water, and he showed that when exposed to the action of decomposing blood it yielded trimethylamine. The results obtained by K. HASEBROEK (*Zeitschrift f. Physiol. Chem.*, **12**, 151, 1888) deserve special mention at this place. He carried on the putrefaction of very dilute solutions of the chloride of choline in the presence of little or no oxygen in HOPPE-SEYLER fermentation flasks. Sewer slime, because of its strong fermentative properties, was used to induce the putrefaction, and calcium carbonate was added to neutralize any acidity that might develop during the fermentation.

The fermentation, as shown by the evolution of gases, lasted for about three months. The total quantity of gas given off was about one litre from 1.17 grams choline chloride. The gases consisted almost entirely of carbonic

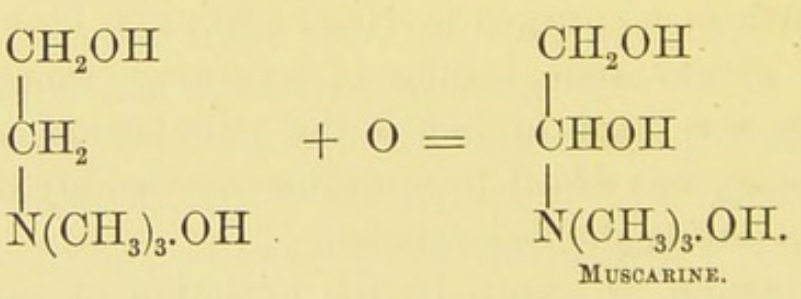
acid and marsh gas. No hydrogen was evolved. When the fermentation ceased the flask was opened and several cubic centimeters of the almost neutral clear liquid were injected under the skin of a rabbit without producing the least effect.

This liquid distilled with alkali gave methylamine and ammonia. What is remarkable about this experiment was the total absence of the higher amines—as, for instance, trimethylamine, which has been observed so many times as a decomposition-product of choline. The absence of any poisonous base, as neurine, was probably largely connected with the absence of oxygen.

Free choline ordinarily forms a strongly alkaline syrup which combines readily with acids to form salts, most of which are deliquescent. By oxidation it is converted into betaine (see page 196), and on treatment with concentrated nitric acid it gives rise to muscarine (see page 198). These reactions can be represented by the equations:



Choline. Betaine.



Muscarine.

By the action of dilute nitric acid choline is converted into a base, the platinochloride of which is efflorescent and

corresponds to the formula $(C_4H_{10}N_2O_3Cl)PtCl_4+2H_2O$. (SCHMIEDEBERG and HARNACK.)

According to MAUTHNER, choline resembles the caustic alkalies in its action. Although putrefying blood decomposes it into trimethylamine, yet, when present in the proportion of 1.4 per cent., it is said to arrest putrefaction. A one to two per cent. solution is said to dissolve fibrin or coagulated albumen on boiling.

The free base, as well as the carbonate, is dimorphous and forms thin plates or long needles.

The CHLORIDE, $C_5H_{14}NO.Cl$, is easily soluble in water and in absolute alcohol (separation from neuridine hydrochloride). It crystallizes over sulphuric acid to needles which readily deliquesce in the air.

The PLATINOCHLORIDE, $(C_5H_{14}NO.Cl)_2PtCl_4$ (Pt = 31.98 per cent.), presents an interesting case of trimorphism. It crystallizes in monoclinic plates (RINNE) which are easily soluble in water, insoluble in alcohol; also in characteristic superposed plates, sometimes in the form of orange-red flat prisms (BRIEGER). From a warm saturated solution containing fifteen per cent. alcohol it crystallizes in regular octahedra; from aqueous solution on slow evaporation in clinorhombic prisms or needles (HOPPE-SEYLER). According to SCHULZE, it sometimes forms beautiful orange-red, chiefly six-sided plates. It contains always more or less water of crystallization which it does not give up completely over sulphuric acid, but only at 110° (BRIEGER). The natural platinochloride becomes strongly electric on rubbing, whereas the synthetic choline double salt does not become electric.

The AUROCHLORIDE, $C_5H_{14}NO.Cl.AuCl_3$ (Au = 44.45 per cent.), is crystalline and is difficultly soluble in cold water, but can be recrystallized from hot water or from

boiling alcohol. It forms prisms, or gold-yellow long needles, which are very easily soluble in hot water and alcohol (LIPPMANN). It can be separated from neuridine aurochloride by its solubility in water (BRIEGER). On heating, the gold salt melts to a brown liquid (SCHULZE) and decomposes at 264°.

The MERCUROCHLORIDE, $C_5H_{14}NO.Cl.6HgCl_2$, is extremely difficultly soluble even in hot water. On this account the mercury salt is very convenient for the separation of choline from accompanying bases.

The PICRATE, $C_5H_{14}NO.OC_6H_2(NO_2)_3$, forms long broad needles which are more easily soluble than neuridine picrate, and hence can be separated by recrystallization. It is more easily soluble in alcohol than in water.

PHYSIOLOGICAL ACTION OF CHOLINE.—Choline was regarded for a long time as physiologically inert, but this belief was set aside by GAEHTGENS (1870), who showed that, when given in large quantity, it possessed a toxic action. This observation of GAEHTGENS has since been confirmed by GLAUSE and LUCHSINGER, BRIEGER, and BOEHM. The chloride of choline produces in animals the same muscarine-like symptoms of poisoning as are developed by the vinyl base neurine, the only difference lies in the intensity of the action. In order to bring about a physiological disturbance, choline must be given in relatively large doses. Thus, BRIEGER has found it necessary to give about 0.1 gram of choline chloride hypodermically to a one kilogram rabbit in order to bring out the same effects as are obtained by the injection of 0.005 gram of the neurine salt. He also found that the fatal dose for a one kilogram rabbit was about 0.5 gram, which is about ten times as large as the fatal dose of neurine chloride. BOEHM observed that doses of 0.025–0.1 gram produced in frogs

general paralysis, which, in a short time, leads to death or recovery; and that in its curara-like paralyzing action, choline resembles artificial muscarine, although the latter is about 500 times stronger. Atropine, as in the case of neurine and muscarine, antagonizes the action of choline. Thus, 0.05 gram of the chloride produced in a frog in one hour diastolic standstill of the heart. This condition was removed by the injection of 0.001 gram of atropine, the heart-beat rising to the normal in about fourteen minutes; 0.05 gram of choline chloride, given subcutaneously to a rabbit (1250 grams) produced salivation, which lasted but a short time, and did not affect the heart-beat and respiration; 0.10 gram was necessary to bring out all the symptoms; 0.05 gram, given to guinea-pigs, had no effect whatever.

Betaine (Oxyneurine), $C_5H_{13}NO_3$.—This base has been well known for some time, because of its occurrence in the vegetable kingdom. Thus, it is present in cotton-seed (Böhm, Ritthausen, Weger); in beet-root juice (Beta vulgaris), and hence in beet-root molasses (Scheibler, 1866). It does not exist in these substances as such, but is formed from a more complex substance by the action of hydrochloric acid or baryta (Liebreich). In this respect it resembles choline, neurine, and probably muscarine. Quite recently, Lippmann (1887) has obtained a lecithin-like body from sugar-beet, which, on heating with baryta, gave oleic acid, glycerine, and phosphoric acid (glycerine-phosphoric acid), and betaine. Betaine, however, does not seem to be a constant constituent, inasmuch as on one occasioned he obtained chiefly choline, and little or no betaine. These two bases also occur together in cotton-seed, and this fact has led Scheibler to the conclusion that it is

no mere chance. Lecithin, as is well known, may contain variable acid constituents (oleic, stearic, palmitic, etc.), and reasoning on this fact, and on the results of his experiments, LIPPMANN has been led to suppose that it may also contain different bases in variable proportions.

It has been obtained from human urine (LIEBREICH, 1869), and from poisonous mussel, but not from putrid mussel (BRIEGER, III., 76). The method for its separation from mussel is described on page 202.

Betaine may be obtained synthetically in several ways: (1) by oxidation of choline with potassium permanganate; (2) by the action of methyl iodide on glycocoll; (3) by treating monochloracetic acid with trimethylamine. The last two methods are of value as indicating the constitution of betaine, and the changes which take place can be represented by the equations:

$$\underset{\text{GLYCOCOLL.}}{\mathrm{NH_2CH_2CO_2H}} + 3\mathrm{CH_3I} = \underset{\text{BETAINE CHLORIDE.}}{\mathrm{N(CH_3)_3ICH_2CO_2H}} + 2\mathrm{HI}$$

$$\underset{\text{MONOCHLORACETIC ACID.}}{\mathrm{CH_2ClCO_2H}} + \mathrm{N(CH_3)_3} = \mathrm{N(CH_3)_3ClCH_2CO_2H}$$

From the formulæ of the salts of betaine it is evident that betaine has properly the composition $C_5H_{13}NO_3$, which is expressed by the structural formula:

$$\mathrm{N(CH_3)_3OHCH_2CO_2H}$$

This free base is, however, readily converted into the anhydride $C_5H_{11}NO_2$.

Betaine is ordinarily regarded as crystallizing with one molecule of water, and the composition is expressed by the formula: $C_5H_{11}NO_2 + H_2O$ (= $OH.N(CH_3)_3.CH_2.CO_2H$). It loses this water of crystallization by heating at 100°, or on standing over sulphuric acid, forming an anhydride of the formula already given. LIEBREICH claims that free betaine possesses the formula $C_5H_{11}NO_2$, because it yields a compound having the composition $(C_5H_{11}NO_2)ZnCl_2$. The free base separates from alcohol in large crystals which deliquesce on exposure to the air. As obtained by BRIEGER from the hydrochloride by treatment with moist silver oxide, it possessed a sweetish taste and neutral reaction. When distilled with potassium hydrate, it yields trimethylamine and other bases, among which a base of the formula $C_8H_{17}NO_5$ occurs in the largest quantity.

The CHLORIDE, $C_5H_{12}NO_2.Cl$, forms beautiful crystals, monoclinic plates, which are permanent in the air, and this can be made use of to effect a separation from the choline salt, which is deliquescent. It is insoluble in absolute alcohol. This fact can be made use of in their separation (LIPPMANN). It can, moreover, be easily separated from other bases by its aurochloride, which is easily soluble. If a little potassio-mercuric iodide is added to a solution of the chloride, there forms a clear yellow oily precipitate, which is soluble in excess, but on rubbing the sides of the tube with a glass rod it reappears as yellow needles. This is said to be a characteristic test (BRIEGER).

The AUROCHLORIDE, $C_5H_{12}NO_2.Cl.AuCl_3$ (Au = 43.10 per cent.), forms magnificent cholesterine-like plates, and is easily soluble (BRIEGER). The aurochloride from sugar-beet is said to crystallize in needles on plates, and to be

difficultly soluble in cold water (SCHEIBLER, LIPPMANN). The double salt of the ptomaine melts at 209°, and in this it coincides with that obtained from beet-sugar, as well as with that of the synthetically prepared base (BRIEGER). The platinochloride is yellow and crystalline.

Betaine is not poisonous.

MUSCARINE, $C_5H_{15}NO_3 = C_5H_{13}NO_2 + H_2O$, the well-known toxic principle which SCHMIEDEBERG obtained from poisonous mushroom (Agaricus muscarius), has been obtained also by BRIEGER (I., 48) from haddock which had been allowed to decompose for five days. The process by which its isolation was effected is described on page 204. This base is specially interesting, because of the relation it bears to choline, for SCHMIEDEBERG has shown that it is formed when choline, or, better still, the platinochloride is oxidized by concentrated nitric acid.

The CHLORIDE, $C_5H_{14}NO_2.Cl$, is obtained on the decomposition of the platinochloride with hydrogen sulphide, as a syrupy residue, which, under the desiccator, shows an inclination gradually to crystallize. It is deliquescent (HARNACK).

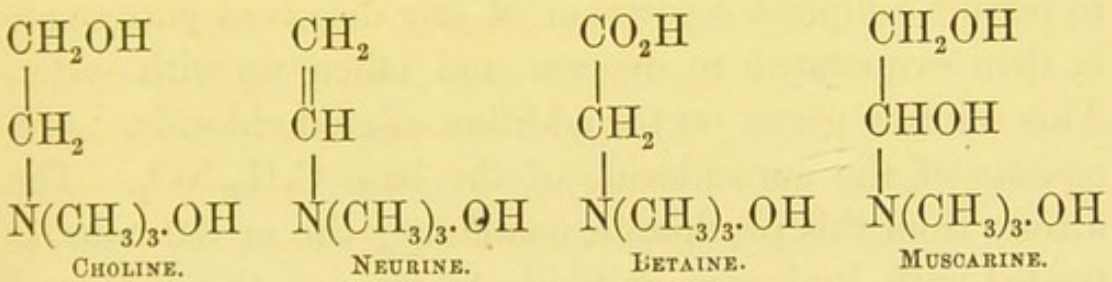
The PLATINOCHLORIDE, $(C_5H_{14}NO_2.Cl)_2PtCl_4$ (Pt = 30.41 per cent.), forms as a crystalline deposit of octahedra, which are difficultly soluble in water. They lose their water of crystallization ($2H_2O$) only on strong heating.

The AUROCHLORIDE, $C_5H_{14}NO_2.Cl.AuCl_3$, crystallizes in needles, and is difficultly soluble in water, more so than the choline double salt (HARNACK).

PHYSIOLOGICAL ACTION.—Small doses of this ptomaine induce in frogs total paralysis, with stoppage of the heart in diastole, and this action is antagonized by subsequent injection of atropine, as well as in the case of previously

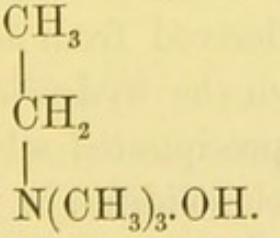
atropinized frogs. Very small doses produce in rabbits profuse salivation and lachrymation, contraction of the pupil, profuse diarrhœa, and passage of urine and semen; finally, the animal dies in convulsions, which, however, are only of short duration.

CONSTITUTION OF THE MEMBERS OF THE CHOLINE GROUP.—The structure of choline was clearly demonstrated by WURTZ, who accomplished the synthesis of this base by treatment of ethylene chlorhydrine with trimethylamine. This same method can be applied to the synthesis of betaine and neurine by using monochloracetic acid and vinylbromide instead of ethylene chlorhydrine. The structural formulæ which can be deduced from these reactions are as follows:



CHOLINE. NEURINE. BETAINE. MUSCARINE.

The formulæ of betaine and muscarine are ordinarily given as the anhydrides, but there can be no doubt that the free bases possess the structure indicated above. All these bases, since they can be prepared from choline, may also be considered as oxidation-products of trimethyl-ethyl-ammonium hydrate:



MYDATOXINE, $C_6H_{13}NO_2$.—This base was obtained by BRIEGER (III., 25, 32) from several hundred pounds of

human internal organs which were allowed to stand in closed but spacious wooden barrels for four months, at a temperature varying from —9° to +5°. He obtained much larger quantities of it, however, from horseflesh which had putrefied under the same conditions. In the process of extraction it is found in the mercuric chloride precipitate together with cadaverine, putrescine, and another base, $C_7H_{17}NO_2$. It can be isolated from this mixture by recrystallizing the mercury salts, which removes the cadaverine because of its difficult solubility in water, and decomposing the soluble mercury salts by hydrogen sulphide. The filtrate freed from mercury is now evaporated to dryness and the residue repeatedly extracted with absolute alcohol, in order to remove putrescine hydrochloride, which is insoluble. The alcoholic solution, after standing some time to permit complete separation of any dissolved putrescine, is then evaporated to dryness and taken up with water. This solution gives, on the addition of gold chloride, a precipitate of the aurochloride of the base $C_7H_{17}NO_2$. The filtrate from this precipitate, containing the mydatoxine, is treated with hydrogen sulphide to remove the gold, and then evaporated to dryness. The colorless, syrupy hydrochloride thus obtained forms with platinum chloride a double salt which is readily soluble in water, and can be purified by repeated recrystallizations from absolute alcohol containing some hydrochloric acid.

The name mydatoxine is derived from μυδάω, to putrefy. The free base is obtained from the hydrochloride by treatment with moist, freshly precipitated silver oxide, as a strongly alkaline syrup, which solidifies in vacuo to plates. It is insoluble in alcohol, ether, etc. It does not distil without decomposition.

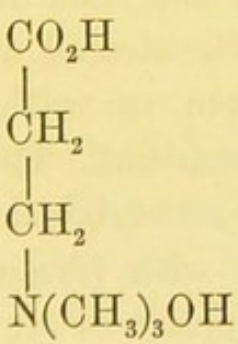
The Hydrochloride, $C_6H_{13}NO_2.HCl$, is a colorless,

deliquescent syrup which does not form any double salt with gold chloride. With platinum chloride it gives an easily soluble salt. Otherwise it combines only with phosphomolybdic acid, with which it forms cubes. Ferric chloride and potassium ferricyanide yield, after a time, Berlin blue. It is readily soluble in alcohol.

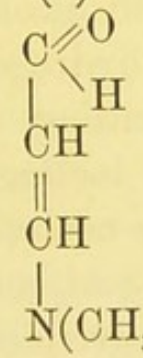
The PLATINOCHLORIDE, $(C_6H_{13}NO_2.HCl)_2PtCl_4$ (Pt= 29.34 per cent.), melts at 193°, with decomposition. It crystallizes in plates which are extremely soluble in water. It can be readily recrystallized from absolute alcohol acidulated with hydrochloric acid. The mercury salt is readily soluble in water.

The exact formula of this base, of mytilotoxine, and some other bases, cannot be considered to be permanently settled, inasmuch as the formula of the hydrochloride, $C_6H_{13}NO_2.HCl$, as deduced from the analysis of the platinum double salt, may equally apply to the base $C_6H_{14}NO_2.OH$ as to the base $C_6H_{13}NO_2$. If the first formula is correct, then mydatoxine is a homologue of betaine, and its structure would be expressed by (1).

(1)



(2)



The second formula would seem to correspond to an unsaturated aldehyde of the choline group and its structure may be indicated by (2).

This ptomaine, although it possesses toxic properties, is not, however, a strong poison. Its action is the same as that

of the base $C_7H_{17}NO_2$ (see page 209), with which it is associated, except that the symptoms of poisoning develop slower, so that the death of a guinea-pig does not take place for about twelve hours. White mice are very susceptible to the action of these two poisons. A short time after the injection of even small doses they are taken with convulsions which come on in paroxysms. The eyeballs roll upward. Lachrymation, diarrhœa, and dyspnœa come on, and the mice die within a short time.

MYTILOTOXINE, $C_6H_{15}NO_2$, is the specific poison of toxic mussel (Mytilus edulis), from which it has been obtained by BRIEGER (III., 76). This poison is formed during the life of the animal under certain conditions which have been thoroughly studied by SCHMIDTMANN, VIRCHOW, and others (see page 38). BRIEGER obtained the poison by extracting toxic mussel with acidulous water, and evaporating this solution to a syrupy consistency. The residue was thoroughly extracted with alcohol, and this solution was treated with lead acetate, in order to remove mucilaginous substances. The filtrate was then evaporated, and the residue extracted with alcohol. Any lead that had dissolved was removed by hydrogen sulphide. The alcohol was expelled, and the resulting syrup was taken up with water and decolored by boiling with animal charcoal. The clear solution was now neutralized with sodium carbonate, acidulated with nitric acid, and precipitated with phosphomolybdic acid. The precipitate was decomposed by warming with neutral lead acetate, and the resulting filtrate, after the removal of the lead by hydrogen sulphide, was acidulated with hydrochloric acid and evaporated to dryness. The residue was extracted with absolute alcohol, whereby betaine, on account of its insolubility, is removed, and the

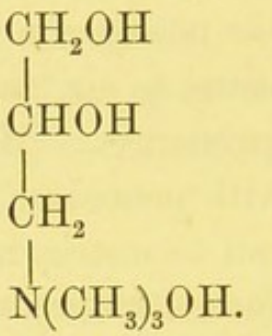
alcoholic solution was precipitated by alcoholic mercuric chloride. The mercury precipitate is repeatedly recrystallized from water, and the poison is obtained as an easily soluble double salt.

The free base as obtained by the addition of alkali to the hydrochloride possesses a disagreeable odor which disappears on exposure to air, and the substance ceases to possess poisonous properties. Mytilotoxine is also destroyed on distillation with potassium hydrate and in the distillate there is found an aromatic non-poisonous product. The free base, therefore, does not exist by itself for any length of time, but soon becomes converted into an inert substance. H. SALKOWSKI has also shown that it is destroyed on boiling with potassium carbonate, whereas its hydrochloric acid solution can be evaporated to dryness and heated to 110° without destroying its poisonous property.

The HYDROCHLORIDE, $C_6H_{15}NO_2.HCl$, prepared from the aurochloride, crystallizes in tetrahedra. It is extremely poisonous and according to BRIEGER produces exactly the same symptoms which have been observed by SCHMIDTMANN in persons who have partaken of poisonous mussels (see page 36). The ordinary alkaloidal reagents produce in its solutions, if at all, only oily precipitates.

As stated under mydatoxine, the formula of the hydrochloride, $C_6H_{15}NO_2.HCl$, is applicable to either one of two bases, $C_6H_{16}NO_2.OH$ or $C_6H_{15}NO_2$. The base corresponding to the first formula is evidently a homologue of muscarine, and should possess a similar physiological action. As a matter of fact, mytilotoxine does resemble muscarine somewhat in its action, and its occurrence together with betaine would seem to make it a decomposition-product of lecithin, in which case this base must be looked upon as a member of the choline group. It is interesting to know

that a compound corresponding to the formula $C_6H_{16}NO_2.OH$ has been known for some time, and was prepared by HANRIOT in a manner analogous to WURTZ'S synthesis of choline, by treating glycerin monochlorhydrine with trimethylamine. This base, trimethyl-glyceryl-ammonium hydrate, has the structure



Unfortunately it has not been studied sufficiently to enable a comparison to be made between it and mytilotoxine.

The AUROCHLORIDE, $C_6H_{15}NO_2.HCl.AuCl_3$ (Au = 41.64 per cent.), crystallizes in cubes. Its melting point is 182°.

It is well to observe that BRIEGER has been unable to obtain this base from mussels that were allowed to putrefy for sixteen days.

PHYSIOLOGICAL ACTION. — According to BRIEGER, mytilotoxine produces all the characteristic effects seen in mussel poisoning, and it is, therefore, a strong paralysis-producing poison, and resembles curara in its action. For the symptoms induced by poisonous mussel see page 36.

GADININE, $C_7H_{17}NO_2$, was found in haddock which was allowed to decompose in open iron vessels for five days during summer. BRIEGER has also obtained it from cultures of the bacteria of human fæces on gelatine. The decomposing mass was thoroughly stirred every day in order to bring it into contact with atmospheric oxygen (BRIEGER, I., 49). It was then treated with water, and hydrochloric acid was added to acid reaction, and after being warmed the mixture was filtered and the filtrate was concentrated

on the water-bath to a syrupy consistency. This syrupy residue was extracted with water, and the aqueous solution was precipitated with a solution of mercuric chloride. The mercuric chloride precipitate contained a base the quantity of which, however, was insufficient for a complete analysis (see page 218). The mercuric chloride filtrate, after the removal of the mercury by hydrogen sulphide, was evaporated to a syrup, and this was then repeatedly extracted with alcohol. The alcoholic solution thus obtained contained neuridine, a base of the same composition as ethylenediamine, muscarine, gadinine, and triethylamine. These bases were separated in the following manner: The alcoholic solution gave with platinum chloride a precipitate of neuridine. The filtrate from this platinum precipitate was heated on the water-bath to expel the alcohol, and then the platinum was removed by hydrogen sulphide. The aqueous filtrate was concentrated to a small volume which, on addition of platinum chloride, gave a precipitate of the isomer of ethylenediamine. The mother-liquor from this precipitate was concentrated on a water-bath, and on cooling the platinochloride of muscarine crystallized out. From the mother-liquor of this precipitate on standing in a desiccator, the gadinine double salt crystallized. The mother-liquor from the gadinine platinochloride was treated with hydrogen sulphide to remove the platinum, and the aqueous filtrate on distillation with potassium hydrate gave triethylamine.

Gadinine (from Gadus callarias, haddock) in small doses does not appear to be poisonous; larger doses (0.5–1 gram) are decidedly toxic and may kill guinea-pigs. The formula of the free base as deduced from the analysis of the platinochloride may be either $C_7H_{17}NO_2$ or $C_7H_{18}NO_2.OH$.

The HYDROCHLORIDE, $C_7H_{17}NO_2.HCl$, as obtained by the decomposition of the platinochloride with hydrogen sulphide, crystallizes under the desiccator in thick colorless needles, which are easily soluble in water; insoluble in alcohol. It forms no combination with gold chloride, but does give crystalline precipitates with phosphomolybdic acid, phosphotungstic acid, and picric acid.

The PLATINOCHLORIDE, $(C_7H_{17}NO_2.HCl)_2PtCl_4$ (Pt = 28 per cent.), is at first quite soluble, and on standing over a desiccator it crystallizes in golden-yellow plates, which, when once formed, are again difficultly soluble in water. It can be recrystallized from hot water.

TYPHOTOXINE, $C_7H_{17}NO_2$.—This base was named thus by BRIEGER (III., 86), and is regarded by him as the specific toxic product of the activity of KOCH-EBERTH'S typhoid bacillus. It is, however, probable that, as in the case of tetanus, there are other basic products formed. He obtained it by cultivating the bacillus on beef-broth for eight to fourteen days at the temperature 37.5°–38°. The nature of the soil on which it grows has a great deal to do with the formation of the poison. An especially important factor is the temperature: for BRIEGER has observed that no poison was produced in one case where the temperature remained by accident at 39° for twenty-four hours. In such cases creatine is present in quantity, whereas otherwise the reverse is the rule.

In the process of extraction it occurs in the mercuric chloride precipitate, and from this it is obtained, after the removal of the mercury by hydrogen sulphide, as an easily deliquescent hydrochloride. This for the purpose of purification is converted into the difficultly soluble aurochloride.

Typhotoxine is isomeric with the body $C_7H_{17}NO_2$, which

BRIEGER obtained from putrefying horseflesh. In its properties it is, however, very different. Thus, the free base is strongly alkaline and its hydrochloride yields a difficultly soluble picrate. On the other hand, the isomer from horseflesh possesses a slightly acid reaction, and does not form a picrate. Again, typhotoxine gives with EHRLICH'S reagent (sulpho-diazobenzole) an immediate yellow color, which disappears upon the addition of alkali, whereas the isomer does not give this reaction. Furthermore, the two bases differ in their physiological action and in their behavior to alkaloidal reagents (see Table I.). Their aurochlorides, however, possess the same melting-point.

The HYDROCHLORIDE is readily deliquescent, and unites with platinum chloride to form an easily soluble double salt crystallizing in needles.

The AUROCHLORIDE, $C_7H_{17}NO_2.HCl.AuCl_3$ (Au=40.45 per cent.), is difficultly soluble, and crystallizes in prisms, which melt at 176°. In its melting-point and solubility it agrees with its isomer from horseflesh. From some of his first experiments in the cultivation of the typhoid bacillus, BRIEGER (II., 69) obtained a basic product differing in some of its characters from typhotoxine. Its aurochloride, on analysis, gave 41.91 and 41.97 per cent. of Au; 16.06 per cent. of C; and 3.66 per cent. of H., whilst typhotoxine aurochloride gave 40.78 per cent. Au; 17.38 per cent. C; and 3.85 per cent. H. For a comparison of the reaction of these two substances see Table I.

In its physiological action, typhotoxine differs from its isomer (page 209) in that the latter produces symptoms with well-marked convulsions, whilst the former throws the animal into more of a paralytic or lethargic condition. The action of this base has been studied only on mice and guinea-pigs. It produces at first slight salivation with

increased respiration; the animals lose control over the muscles of the trunk and extremities, and fall down helpless upon their sides. The pupils become strongly dilated, and cease to react to light; the salivation becomes more profuse; the rate of heart-beat and of respiration gradually decreases, and death follows in from one to two days. Throughout the course of these symptoms the animals have frequent diarrhœic evacuations, but at no time are convulsions present. On post-mortem, the heart is found to be contracted in systole, the lungs are strongly hyperæmic, the other internal organs pale, the intestines firmly contracted, and their walls pale.

A BASE (?) $C_7H_{17}NO_2$ was obtained by BRIEGER (III., 28) on working over about one hundred pounds of horse-flesh which had been allowed to undergo slow putrefaction with limited access of air and at a low temperature (—9° to +5°) for four months. It occurs in the mercuric chloride precipitate together with cadaverine, putrescine, and mydatoxine, and from these bases it can be separated and isolated according to the method on page 200.

The free substance possesses, even after most careful purification, a slightly acid reaction. This acidity is removed from even a large quantity of the substance by the addition of a drop of alkali. On account of the acid character of the free substance, BRIEGER does not consider it to be a base (a ptomaine). It differs, however, from the amido-acids in its poisonous character; in the fact that, unlike an acid, it does not unite with bases to form salts; and in not giving the characteristic red coloration (HOFMEISTER'S reaction for the amido-acids) with ferric chloride. Whatever the true nature of this substance may be, it nevertheless, in its other properties, behaves like a base.

Thus, it forms simple as well as double salts. On boiling with copper acetate, it gives amorphous floccules. Under the desiccator it solidifies into plates which deliquesce on exposure to the air. It does not combine either with silver oxide or with cupric hydrate. On dry distillation it yields a distillate possessing a strong acid reaction and a peculiar odor. The distillate does not give any precipitate with platinum chloride, or with gold chloride, nor does it react with copper acetate. With phosphomolybdic acid, however, it forms an amorphous mass; with ferric chloride and potassium ferricyanide it yields an immediate precipitate of Berlin-blue, whereas the original substance does not give any blue coloration.

The HYDROCHLORIDE, $C_7H_{17}NO_2.HCl$, crystallizes in fine needles which are insoluble in absolute alcohol. When its aqueous solution is treated with freshly precipitated silver oxide, the resulting filtrate contains some silver oxide in solution, from which it can be removed by hydrogen sulphide; thus differing from an ammoniacal silver solution, which gives no precipitate on treatment with hydrogen sulphide. In this respect it resembles SALKOWSKI'S base, page 178. For reactions of the hydrochloride, see Table I.

The AUROCHLORIDE, $C_7H_{17}NO_2.HCl.AuCl_3$ (Au= 40.45 per cent.), forms plates which are difficultly soluble in water, and melt at 176°. It is dimorphous, since sometimes it is also obtained in needles which can be changed into plates.

PHYSIOLOGICAL ACTION.—This substance, when injected into frogs, produces a curara-like action. A few minutes after the injection the animal falls into a condition of paralysis, and, although it can still react toward reflexes, it cannot move from its place. At times fibrillary twitchings pass over the body. The pupils dilate, the heart-action

becomes gradually weaker, and finally, after several hours, the animal dies, with the heart in diastole. Doses of 0.05 to 0.3 gram of the hydrochloride, injected into guinea-pigs, produce in a short time a slight tremor, gradual increase in respiration, and slight moistening of the lower lip. The pupils at first contract, then dilate ad maximum, and become reactionless. The temperature remains at first normal; chills of short duration follow in rapid succession. The animal squats on the ground with its snout pressing against the floor in exactly similar manner as is caused by the mussel poison. Violent clonic convulsions follow in continually shorter intervals, and at the same time lachrymation and salivation become profuse, but not as excessive as in the case of the muscarine-like ptomaines. The temperature sinks with the decrease in the rate of respiration, the ears previously gorged become pale and cold, and the heart-action becomes irregular and less frequent than before. General paralysis sets in, but the head still moves upward and backward. External stimuli induce violent clonic convulsions, the animal repeats frequently choking movements, and at the same time yields large quantities of saliva; finally, it falls upon its side completely paralyzed, and dies. The heart stops in diastole, the intestines are pale and strongly contracted, and the bladder is empty and likewise contracted.

A Base $C_5H_{12}N_2O_4$ was obtained by Pouchet (1884) from the residual liquors resulting from an industrial treatment of débris of bones, flesh, and waste of all kinds, with dilute sulphuric acid. It is accompanied by another base, $C_7H_{18}N_2O_6$, from which it can be separated by treatment with alcohol. The base itself forms tufts of delicate needles which alter or decompose less easily than the accompanying

base. The platinochloride, $(C_5H_{12}N_2O_4.HCl)_2PtCl_4$, forms a dull yellow powder, somewhat soluble in strong alcohol, but insoluble in ether.

The hydrochlorides of these bases form silky needles which are altered by excess of hydrochloric acid and by exposure to air. POUCHET considers them to be closely allied to the oxy-betaines. The general alkaloidal reagents precipitate these bases; the phosphomolybdic precipitate, on addition of ammonia, gives a blue tint. Both bases are toxic, and exert a paralyzing action upon the reflex movements.

The method employed by POUCHET for their isolation was to precipitate them as tannates. The precipitate was decomposed by lead hydrate in the presence of strong alcohol, the excess of lead removed from the solution by hydrogen sulphide, and the clear liquid thus obtained was submitted to dialysis. The above bases occurred in the dialysate.

TETANINE, $C_{13}H_{30}N_2O_4$, was obtained by BRIEGER (III., 94) by cultivating impure tetanus microbes of ROSENBACH, in an atmosphere of hydrogen on beef-broth for eight days at 37°–38°. It likewise occurs in cultures on brain-broth. Quite recently (April, 1888), BRIEGER has succeeded in obtaining tetanine from the amputated arm of a tetanus patient, identical in its physiological action and chemical reactions with that isolated from cultures of ROSENBACH'S germs on beef-broth. The presence of tetanine during life in tetanus patients has thus been demonstrated. It has not been found in the brain and nerve tissue of persons dead from tetanus. A portion of the jelly-like mass taken from the amputated arm was found to contain tetanus bacilli as well as staphylococci and streptococci, and when planted

on beef-broth, tetanine was formed, but no tetanotoxine or spasmotoxine.

For its isolation BRIEGER employed the following method. The cultures were slightly acidulated with hydrochloric acid, heated, and filtered; the filtrate was then treated with lead acetate and with alcoholic mercuric chloride in the manner described under mytilotoxine (page 202). The filtrate from the mercuric chloride precipitate contains the greater part of the active principle, provided the precipitate has been thoroughly washed. After the removal of the mercury by hydrogen sulphide, it is evaporated and the residue is repeatedly extracted with absolute alcohol, in which the tetanus poison readily dissolves, and can thus be separated from the insoluble ammonium chloride. The alcoholic solution is treated with alcoholic platinum chloride, which precipitates the ammonium and creatinine platinochlorides, whilst the platinochloride of the poison remains in solution. The filtrate from this precipitate gives, on the addition of ether, a flocculent precipitate possessing exceedingly deliquescent properties. The precipitate is, therefore, rapidly filtered off by means of a pump, and dried in vacuum. It can then be recrystallized from hot ninety-six per cent. alcohol, and the beautiful clear yellow plates thus obtained, if dried again in vacuum, become rather difficultly soluble in water, from which it can then be recrystallized and obtained in a perfectly pure condition.

Phosphomolybdic acid cannot be used in the separation of tetanine, inasmuch as it destroys the poison (BRIEGER). BOCKLISCH has also observed that it destroys the poison formed in the putrefaction of fish.

Tetanine obtained by treating the hydrochloride with

freshly precipitated moist silver oxide, forms a strongly alkaline yellow syrup. With alkaloidal reagents it gives the same reactions as the hydrochloride, except that it does not give a blue color with ferric chloride and potassium ferricyanide. It is easily decomposed in acid solution, but is permanent in alkaline solution.

The HYDROCHLORIDE, $C_{13}H_{30}N_2O_4.2HCl$, is deliquescent and is easily soluble in absolute alcohol. Besides with platinum, it combines only with phosphomolybdic acid to form an easily soluble crystalline precipitate, which on the addition of ammonium hydrate becomes white. If, however, the hydrochloride is impure, phosphomolybdic acid produces a precipitate which is colored an intense blue by ammonia. Potassium-bismuth iodide yields a precipitate which is at first amorphous, but soon becomes crystalline. Ferric chloride and potassium ferricyanide produce a slowly developing blue color which probably is due to impurities.

The PLATINOCHLORIDE, $C_{13}H_{30}N_2O_4.2HCl.PtCl_4$ (Pt = 28.65 per cent.), is easily soluble in absolute alcohol from which it is precipitated on the addition of ether. From ninety-six per cent. alcohol it crystallizes in clear yellow plates. After repeated recrystallization from alcohol and drying in vacuum it becomes difficultly soluble in water so that it can be recrystallized from the latter. It decomposes at 197°.

This base produces the characteristic, though probably not all the symptoms of tetanus, since we know of at least three other toxines (page 148) which occur with tetanine in cultures of the tetanus microbe. The symptoms induced by relatively large doses in warm-blooded animals, as mice, guinea-pigs, and rabbits, exhibit two distinct phases. In the first, the animal is thrown into a lethargic paralytic condition, then suddenly becomes uneasy, and the respira-

tion becomes more frequent. This is followed by the second phase, in which tonic and clonic convulsions, especially the former, predominate till death results. Small doses do not seem to affect guinea-pigs, whilst frogs seem to be much less sensitive than mice. The characteristic convulsions and opisthotonus seen in tetanus in man, are also produced in guinea-pigs on injection of large doses of this base. Dogs and horses seem to be but slightly sensitive to the action of this poison.

A Base $C_{14}N_{20}N_2O_4$ was isolated by Guareschi from putrid fibrin. We have been unable to obtain any description of this compound.

A Base $C_7H_{18}N_2O_6$ was isolated by Pouchet in 1884. It is said to form short, thick prisms which become brown when exposed to light.

The Platinochloride, $(C_7H_{18}N_2O_6.HCl)_2PtCl_4$, crystallizes in prismatic needles which are insoluble in strong alcohol. For further details in regard to this base see page 210.

Tyrotoxicon has been obtained in poisonous cheese (Vaughan, Wallace, Wolff), in poisonous ice-cream (Vaughan, Novy, Schearer, Ladd), in poisonous milk (Vaughan, Novy, Newton, Wallace, Firth, Schearer), and in cream-puffs (Stanton). The methods of separating this poison and its effects upon animals have already been given with sufficient detail. Chemically, it is very unstable. When warmed with water to about 90°, it decomposes. Hydrogen sulphide also decomposes it, therefore all attempts to isolate it by precipitation with some base, such as mercury or lead, and then removing the base

with hydrogen sulphide, have failed. Its unstable character is illustrated by the fact that it may disappear altogether within twenty-four hours from milk rich in the poison which is allowed to stand in an open beaker.

With potassium hydrate it forms a compound which agrees in crystalline form, chemical reactions, and the per cent. of potassium which it contains, with the compound of diazobenzole and potassium hydrate. This substance is best obtained from milk containing tyrotoxicon as follows: The filtered milk, which is acid in reaction, is neutralized with sodium carbonate, agitated with an equal volume of ether, allowed to stand in a stoppered glass cylinder for twenty-four hours, the ether removed, and allowed to evaporate spontaneously from an open dish. The aqueous residue is acidified with nitric acid, then treated with an equal volume of a saturated solution of potassium hydrate, and the whole concentrated on the water-bath (this compound is not decomposed below 130°). On being heated the mixture becomes yellowish-brown, and emits a peculiar aromatic odor. On cooling the tyrotoxicon compound forms in beautiful, six-sided plates along with the prisms of potassium nitrate.

With equal parts of sulphuric and carbolic acids, pure tyrotoxicon gives a green coloration, but in whey the color varies from yellow to orange-red. This color reaction may be used as a preliminary test in examining milk for tyrotoxicon. It is best carried out as follows: Place on a clean porcelain surface two or three drops each of pure carbolic and sulphuric acids. Then add a few drops of the aqueous solution of the residue left after the spontaneous evaporation of the ether. If tyrotoxicon be present, a yellow to an orange-red coloration will be produced. This test is to be regarded only as a preliminary one, for the coloration may

be due to the presence of a nitrate or nitrite. The tyrotoxicon must be converted into the potassium compound and purified before the absence of nitrate or nitrite can be positively demonstrated. Moreover, the physiological test should always be made in testing for this poison.

With platinum chloride in alcoholic solution tyrotoxicon forms a compound which explodes with great violence at the temperature of the water-bath. This also corresponds with the compound of platinum chloride and diazobenzole.

Pure tyrotoxicon is insoluble in ether, and its extraction from alkaline solutions by this solvent is due to the presence of foreign matter, with which the poison is taken up by the ether.

The physiological action of this ptomaine has been sufficiently discussed in a preceding chapter.

MYDALEINE (*μυδάλέος*, putrid) is a poisonous base obtained from putrefying cadaveric organs, liver, spleen, etc. (BRIEGER, II., 31, 48). Though it is apparently present on about the seventh day, it is unobtainable until about the third or fourth week. The method for its separation from the accompanying bases is given under saprine (page 169). It is liable to occur in the mercuric chloride filtrate as well as in the precipitate, inasmuch as the double salt is insoluble only in perfectly absolute alcohol. In order to purify the platinochloride as obtained on page 169, it is repeatedly recrystallized from a very small quantity of lukewarm water. This base has not been obtained in sufficient quantity to permit a complete determination of its composition. It is probably a diamine, containing four or five carbon atoms, and hence is nearly related to some of the diamines already described.

The PLATINOCHLORIDE, on analysis, gave: Pt=38.74,

C=10.83, H=3.23. It crystallizes in small needles, and is extremely soluble in water.

The HYDROCHLORIDE crystallizes with extreme difficulty, even on standing for some time in a desiccator. On exposure to the air it rapidly deliquesces.

PHYSIOLOGICAL ACTION.—Mydaleine has an entirely specific action. Small quantities injected into guinea-pigs or rabbits produce, after a short time, a moistening of the under lip, and an abundant flow of secretion from the nose and eyes. The pupils dilate gradually to maximum, and become reactionless; the ear vessels become strongly injected, and the body temperature rises 1° to 2°. The hairs bristle, and the animal occasionally shudders. Gradually the salivation ceases, the respiration and heart-action, which were at first hastened, now decrease, the temperature falls, the ears become pale, and the animal finally recovers. During the action of the poison the animal shows a tendency to sleep, and the peristaltic action of the intestines is heightened. Larger doses (0.050 gram) induce an exceedingly violent action, which invariably results in the death of the animal. On post-mortem, the heart is found to be stopped in diastole, and the intestines and bladder contracted; otherwise nothing abnormal is observed.

A TOXIC BASE.—From human livers and spleens which were decomposing for two weeks in thorough contact with air there was isolated, besides cadaverine and putrescine, a small quantity of a poisonous base (BRIEGER, II., 29, 48). The mercuric chloride precipitate was decomposed, and the hydrochlorides were precipitated by gold chloride (to remove cadaverine, which is soluble), and the aurochloride was then changed into the platinum salt, whereby the insoluble

putrescine platinochloride was removed. In the mother-liquors from the putrescine salt an easily soluble platinum compound was separated, and found to contain 41.30 per cent. Pt. It crystallized in fine needles. The hydrochloride forms small, readily deliquescent needles, and does not produce a precipitate in alcoholic platinum chloride. Injected into guinea-pigs and rabbits it induced an exalted peristaltic action of the intestines, which lasted several days, and produced in the animals, on account of the continuous evacuations, a condition of great weakness. No disturbance in the functions of the other organs was observed.

A Base was isolated from decomposing haddock which were exposed for five days during summer in an open iron vessel. Brieger (I., 42) found in the aqueous mercuric chloride precipitate (see page 205) a base the hydrochloride of which crystallized in well-formed, small needles. The platinochloride likewise crystallized in beautiful needles, and gave, on analysis, 36.03 per cent. of Pt; 7.81 per cent. of N.

A substance of muscarine-like action was obtained by Brieger (I., 59) from putrefying gelatine, ten days at 35°, though in insufficient quantity to permit a determination of its character. The residue containing this substance gave, on distillation with alkali, only ammonia.

A Base was obtained by Bocklisch (III., 52, 53) from herring which had undergone putrefaction for twelve days. It was found in the distillate, together with trimethylamine and dimethylamine, obtained by distilling the mercuric chloride filtrate, after the removal of the mercury, with sodium hydrate. The platinochloride was easily

soluble, and crystallized in large thin plates. On analysis, it gave: Pt=28.57, C=22.34, H=4.66. The hydrochloride is easily soluble in water, and in absolute alcohol, and besides with platinum gives only with phosphomolybdic acid a yellow precipitate which is soluble in excess, and with ammonia gives an immediate blue color. It immediately reduces a mixture of ferric chloride and potassium ferricyanide with formation of Berlin blue; and similarly throws down metallic gold from solutions of gold chloride.

From poisonous mussel, BRIEGER (III., 79) obtained an aurochloride of a base crystallizing in needles. The quantity isolated was insufficient for analysis. It is interesting because of its property of inducing salivation, a symptom which has been observed by SCHMIDTMANN and by CRUMPE in some cases of mussel poisoning.

A BASE was obtained by GUARESCHI and MOSSO (*Journ. für Praktische Chem.*, **28**, 508) from fresh ox-flesh in the alkaline ether extract obtained by DRAGENDORFF'S method. It formed a yellowish alkaline fluid, of unpleasant odor, and after a time gave a deposit of microscopic crystals. The hydrochloride gave the following reactions: Gold chloride, yellow crystalline precipitate; platinum chloride, precipitate; potassium iodide and iodine in hydriodic acid, kermes-red precipitate; phosphotungstic acid, nothing; phosphomolybdic acid, an abundant yellow precipitate; tannic acid, heavy, grayish precipitate; same with MAYER'S reagent; picric acid, yellow precipitate; MARMÉ'S reagent, precipitate soluble in excess; potassium bichromate, nothing; potassium permanganate and sulphuric acid, violet color; potassium ferricyanide and ferric chloride, Prussian blue precipitate.

By giving a precipitate with tannin, and not with phosphotungstic acid, it resembles neurine.

Ch. Gram has studied the decomposition of yeast under the influence of an infusion of hay. The yeast was allowed to putrefy for fourteen days, and was then treated with zinc sulphate. The latter was precipitated by barium hydrate, and the filtrate, after the removal of the barium by sulphuric acid, was evaporated to dryness, and extracted with absolute alcohol. The alcoholic solution was evaporated, and the residue again extracted with alcohol. The extraction residue was taken up with water, and again subjected to the above treatment with zinc sulphate, barium hydrate, etc.

The filtrate was poisonous, and produced, in frogs, paralysis and stoppage of the heart in diastole. Addition of platinum chloride and alcohol precipitated two bases. One of these, although possessing a curara-like action, did not affect the heart. When its solution was heated for twenty-four hours on the water-bath, it caused general paralysis and stoppage of the heart. The platinochloride contained 38.05 per cent. of platinum.

The other base also possessed a slight curara-like action, and its platinochloride gave, on analysis, 40.92 and 39.4 per cent. of platinum.

Brieger found a basic substance in small quantities in cultures of the staphylococcus pyogenes aureus on bouillon and beef-broth (II., 74). The hydrochloride formed groups of colorless, non-deliquescent needles. With platinum chloride it yielded a double salt, crystallizing in needles, and containing 32.93 per cent. of Pt. For its reactions, see Table I.

A Base—boiling-point about 284°—was obtained by Brieger (II., 61) from human livers and spleens which were putrefying for two to three weeks. It occurs in the mercuric chloride filtrate, as described under saprine, page 169, together with some mydaleine, trimethylamine, and hydrocarbons. The filtrate, after the mercury is removed by hydrogen sulphide, is evaporated to dryness, and finally the last traces of water are removed in a vacuum. The residue is then treated with absolute alcohol, and from this alcoholic solution the mydaleine is precipitated by the addition of alcoholic mercuric chloride. The trimethylamine is separated by distillation of the alkaline filtrate, previously deprived of its mercury by hydrogen sulphide; whilst the mother-liquor yields an oily mixture of hydrocarbons and bases. The latter were separated by fractional distillation, whereby only one of the bases was obtained in sufficient quantity for study. It boiled at about 284°, and gave, with hydrochloric acid on evaporation, a salt crystallizing in beautiful, long needles, which were very easily soluble in perfectly absolute alcohol. With gold chloride and picric acid it gave only oily products; with ferric chloride and potassium ferricyanide, an intense blue; with platinum chloride, an extremely easily soluble double salt, which appeared under the microscope in the form of very fine needles, whilst from alcohol-ether the double salt slowly separated in thin plates which contained 30.36 per cent. of platinum. The free base shows a slight fluorescence. It is not poisonous, and, according to Brieger, is probably a pyridine derivative.

Other non-poisonous bases were present in very small quantity in the mother-liquor described above, after the separation of the oily mixture.

PEPTOTOXINE.—By this name BRIEGER (I., 14–19) has designated a poisonous base which he has found in some peptones, and hence in the digestion of fibrin; in putrefying albuminous substances, such as fibrin, casein, brain, liver, and muscles. It is a well-known fact that animal tissues, in the early stages of putrefaction, possess strong toxic properties, even before the decomposition could have advanced far enough to effect a splitting-up of the proteid and carbohydrate molecules. BRIEGER and others have tried to seek an explanation of this toxicity by connecting it with an early peptonization of the proteids brought about by the action of ferments which are distributed throughout the tissues, and which begin their activity immediately after death. This poison has not been definitely isolated, but its general properties and action have been studied by BRIEGER and SALKOWSKI. The former prepared it by digesting fibrin for twenty-four hours with gastric juice at the temperature of the blood. The perfectly fresh peptone thus obtained was evaporated to a syrupy residue, and this was then extracted with boiling alcohol. The residue left on evaporation of the alcoholic solution was digested for some time with amyl alcohol, which on subsequent evaporation gave amorphous brownish masses. This extract can now be purified by neutral lead acetate. The filtrate, after the removal of the lead by hydrogen sulphide, is repeatedly extracted with ether, then evaporated to dryness, and extracted as before, with amyl alcohol. This final extract is evaporated to drive off the alcohol, taken up with water, and filtered. The colorless aqueous solution thus obtained contains the poisonous substance, which, however, can only with extreme difficulty be brought to crystallization in vacuum.

This poison, when in its purest condition, as shown by

its failure to give the biuret reaction, possesses a neutral reaction. Its behavior to Millon's reagent is quite characteristic: it gives a white precipitate, which on boiling becomes intensely red. From this reaction, BRIEGER is inclined to regard this substance as a hydroxyl or an amido-derivative of benzole. The ptomaine can be extracted from acid as well as alkaline solution by amyl alcohol; more difficult, in the cold, than on heating. It is absolutely insoluble in ether, benzole, and chloroform; very soluble in water. It is not destroyed by boiling, by passing hydrogen sulphide, or by strong alkalies; but is destroyed, however, when the putrefaction lasts longer than eight days. For its behavior to reagents, see Table I.

Various observers have shown that peptone possesses a toxic action, and some have been led to regard this toxicity as not due to the peptone itself but rather to the presence of this or some other ptomaine. At least BRIEGER found one specimen of dry Witte's peptone to be perfectly harmless; whereas, the fresh peptone formed by fibrin digestion possessed strong toxic powers. Moreover, this non-poisonous peptone when exposed to the action of gastric juice was found to yield the poisonous substance. The poisonous nature of proteids, and the physiological action of this base will be described later.

Table of Ptomaines.

Formula	Name.	Discoverer.	Physiological action.[1]
$C\ H_5\ N$	Methylamine.	.....	Non-poisonous.
$C_2\ H_7\ N$	Dimethylamine.	.....	" "
$C_3\ H_9\ N$	Trimethylamine.	.....	" "
$C_2\ H_7\ N$	Ethylamine.	.....	" "
$C_4\ H_{11}N$	Diethylamine.	....	" "
$C_6\ H_{15}N$	Triethylamine.	.....	" "
$C_3\ H_9\ N$	Propylamine.	.....	
$C_5\ H_{13}N$	Amylamine.	.....	
$C_6\ H_{15}N$	Hexylamine.	.....	
$C_5\ H_{11}N$ (?)	Tetanotoxine.	Brieger.	Poisonous.
$C_8\ H_{11}N$	Collidine (?).	Nencki.	
$C_8\ H_{13}N$	Hydrocollidine (?).	Gautier and Etard.	Poisonous.
$C_9\ H_{13}N$	Parvoline (?).	" " "	
$C_{10}H_{15}N$	Unnamed.	Guareschi and Mosso.	Poisonous.
$C_2\ H_8\ N_2$	Ethylidenediamine (?).	Brieger.	"
$C_3\ H_8\ N_2$	Trimethylenediamine.	"	"
$C_4\ H_{12}N_2$	Putrescine.	"	Non-poisonous.
$C_5\ H_{14}N_2$	Cadaverine.	"	" "
$C_5\ H_{14}N_2$	Neuridine.	"	" "
$C_5\ H_{16}N_2$	Saprine.	"	" "
$C_7\ H_{10}N_2$	Unnamed.	Morin.	" "
$C_2\ H_7\ N_3$	Methyl-guanidine.	Brieger.	" "
$C_{13}H_{20}N_4$	Unnamed.	Oser.	
$C_{17}H_{38}N_4$	"	Gautier and Etard.	
$C_8\ H_{11}N\ O$	Mydine.	Brieger.	Non-poisonous.
$C_5\ H_{13}N\ O$	Neurine.	"	Poisonous.
$C_5\ H_{11}N\ O_2$	Unnamed	E. and H. Salkowski.	Non-poisonous.
$C_5\ H_{15}N\ O_2$	Choline.	Brieger.	Poisonous.
$C_5\ H_{13}N\ O_3$	Betaine.	"	Non-poisonous
$C_5\ H_{15}N\ O_3$	Muscarine.	"	Poisonous.
$C_6\ H_{13}N\ O_2$	Mydatoxine.	"	"
$C_6\ H_{15}N\ O_2$	Mytilotoxine	"	"
$C_7\ H_{17}N\ O_2$	Gadinine.	"	Non-poisonous.
$C_7\ H_{17}N\ O_2$	Typhotoxine.	"	Poisonous.
$C_7\ H_{17}N\ O_2$	Unnamed	"	"
$C_5\ H_{12}N_2O_2$	"	Pouchet.	"
$C_{14}H_{20}N_2O_4$	"	Guareschi.	
$C_{13}H_{30}N_2O_4$	Tetanine	Brieger.	Poisonous.
$C_7\ H_{18}N_2O_6$	Unnamed.	Pouchet.	"
	Tyrotoxicon.	Vaughan.	"
	Mydaleine.	Brieger.	"
	Spasmotoxine.	"	"
	Peptotoxine.	"	"

[1] Only those bases are here denoted as poisonous which possess a decided toxicity.

CHAPTER VII.

CHEMISTRY OF THE LEUCOMAINES.

Under this head are classed those basic substances which are found in the living tissues, either as the products of fermentative changes or of retrograde metamorphosis. Most of these substances have already been known for many years, though their real significance as alkaloidal bodies, and their relation to the functional activities of the animal organism have been but little understood, or rather they have not been brought together under the leading conception that they are alkaloidal products of physiological change. The first attempt at the systematic study and generalization of these basic substances was made by GAUTIER, who applied to them the name leucomaines, a term derived from the Greek λεύχομα, signifying white of eggs. Under this name he includes all those basic substances which are formed in animal tissues during normal life, in contradistinction to the ptomaines or basic products of putrefaction. The distinction between vegetable and animal alkaloids is not very well defined, and, in fact, there seem to be reasons for considering their formation as due to the same causes which bear an intimate relation to the physiology of the cells and tissues of both kingdoms. Thus, vegetable tissues are known to contain not only definite ptomaines such as choline, but also leucomaines as hypoxanthine, xanthine, etc. Indeed, in this latter group must be placed, on account of their relation to xanthine, those well-defined alkaloidal bases, caffeine and theobro-

mine. Not only are the representatives of these two divisions of basic substances common to both kingdoms, but their parent bodies, lecithin, nuclein, etc., are known to occur in both, thus giving rise to the same bases on decomposition.

So far as the genesis of most of the leucomaines is concerned, we know very little, though GAUTIER is of the belief that they are being formed continuously and incessantly in the animal tissues, side by side with the formation of urea and carbonic acid, and at the expense of the nitrogenous elements. BOUCHARD has sought an explanation of the presence of these bases in the urine, by supposing that they were originally formed in the intestinal tract, from which they were absorbed into the system, to be subsequently eliminated by the kidneys. This view has also been brought forward by SCHÄR (1886), who holds that these bases, which may be formed by putrefactive changes in the intestinal tract, are absorbed into the circulatory system, whence they may be partly eliminated by the kidneys or may be partly deposited in the tissues themselves.

The leucomaines proper can be divided into two distinct and well-defined groups: (1) the Uric Acid Group, and (2) the Creatinine Group.

The first of these divisions contains a number of well-known bases which are closely related to uric acid. The order in which they will be described is as follows:

Adenine,	$C_5H_5N_5$.
Hypoxanthine,	$C_5H_4N_4O$.
Guanine,	$C_5H_5N_5O$.
Xanthine,	$C_5H_4N_4O_2$.
(Uric Acid,	$C_5H_4N_4O_3$.)

Heteroxanthine, $C_6H_6N_4O_2$.
Paraxanthine, $C_7H_8N_4O_2$.
Carnine, $C_7H_8N_4O_3$.
Pseudoxanthine, $C_4H_5N_4O$.
Spermine, C_2H_5N.

The members of the second group have all been discovered by GAUTIER, and by him are regarded as allied to creatine and creatinine. These two substances, especially the latter, have been hitherto regarded as strongly basic in character, but SALKOWSKI has recently shown that creatinine, when perfectly pure, possesses little or no alkaline reaction, and, moreover, does not combine with acids. The bases in this group are :

(Creatinine, $C_4H_7N_3O$.)
(Creatine, $C_4H_9N_3O_2$.)
Cruso-creatinine, $C_5H_8N_4O$.
Xantho-creatinine, $C_5H_{10}N_4O$.
Amphi-creatine, $C_9H_{19}N_7O_4$.
Base, $C_{11}H_{24}N_{10}O_5$.
Base, $C_{12}H_{25}N_{11}O_5$.

Besides these two general classes of leucomaines, there may be made a third class of undetermined leucomaines, embracing those bases which have been observed, but studied more or less incompletely, in the various physiological secretions of the body.

LEUCOMAINES OF THE URIC ACID GROUP.

ADENINE, $C_5H_5N_5$, which has been recently (1885) discovered by KOSSEL, forms the simplest member of the uric acid group of leucomaines, and as such it deserves special attention, inasmuch as it shows most clearly the

relation that exists between hydrocyanic acid and the members of this group. This base is apparently formed by the polymerization of hydrocyanic acid,—a view that is confirmed, at least in part, by the fact that on heating with potassium hydrate to 200°, it yields a large quantity of potassium cyanide. Moreover, by the action of reducing agents it is converted into a substance similar to, if not identical with azulmic acid. It has not been prepared synthetically, though GAUTIER has claimed to have synthesized two closely related bodies, xanthine and methyl-xanthine, by simple heating of hydrocyanic acid in a sealed tube in contact with water and a little acetic acid.

This base was first prepared from pancreatic glands—hence the term adenine, which is derived from the Greek word *αδήν*, meaning a gland. It has since been shown to occur together with guanine, hypoxanthine, etc., as a decomposition-product of nuclein, and, therefore, it may be obtained from all tissues and organs, animal or vegetable, rich in nucleated cells. Accordingly, it has been found in the kidneys, spleen, pancreatic and lymphatic glands, in beer-yeast, and tea-leaves. In the latter, adenine appears to exist in a preformed condition, since it can be extracted without the use of acid reagents. It has also been observed in the liver and urine of leucocythæmic patients; its occurrence in this disease will be readily understood when it is remembered that leucocythæmia is characterized by the presence in the blood of an unusual proportion of the nucleated white blood corpuscles, which, owing to various unfavorable conditions become destroyed in time, and the contained nuclein, as a result, splits up into adenine and guanine. These two bases may, therefore, be expected in all pathological conditions where there is an abnormal accumulation of pus. Indeed, as early as 1865,

NAUNYN extracted from pus, obtained from the pleural cavity, a considerable quantity of a substance which probably was either adenine or guanine, or both. Adenine does not occur, or only in minute traces, in meat extract; and in this it resembles guanine, which is present only in traces. KOSSEL explains this fact on the ground that the muscle tissue is very poor in nucleated cells, *i. e.*, in nuclein. It would seem that the muscle cell in losing the morphological character of a cell has also suffered a corresponding loss in its chemical properties. For while the decomposition-products of nuclein—hypoxanthine, xanthine, phosphoric acid, etc.—are found in the muscle tissue, they do not exist in combination as they do in the nuclein molecule. This is seen in the fact that the bases exist in the free condition, since they can be extracted by water; and again, the phosphoric acid is present in the muscle tissue, not in organic combination, but as a salt. In the nucleated cell, adenine, guanine, etc., do not exist in the free condition but form, in part at least, with albumen and phosphoric acid, a loose combination which is readily decomposed by the action of acids at the boiling temperature. This same change takes place spontaneously after death.

There can be no doubt that adenine and guanine play an important part in the physiological function of the cell nucleus, which, from recent observations, appears to be necessary to the formation and building up of organic matter. It is now known that non-nucleated cells, though capable of living, are not capable of reproduction. We must look, therefore, to the nucleus as the seat of the functional activity of the cell—indeed, of the entire organism. Nuclein, the parent substance of adenine and guanine, is the best known, and probably most important constituent of the nucleus, and as such it has been already credited

with a direct relation to the reproductive powers of the cell. This chemical view has recently been confirmed by ZACHARIAS, who showed that chromatin of histologists is identical with nuclein.

The method employed by KOSSEL for the preparation of adenine, is as follows: The finely divided pancreatic glands are heated to boiling, for three to four hours, with a large quantity of dilute sulphuric acid (0.5 per cent. by volume of concentrated acid), and the acid solution thus obtained is treated with a slight excess of hot concentrated baryta water. The excess of baryta is removed by carbonic acid, and the solution is then filtered; the filtrate is concentrated to a small bulk, about 100 c. c., rendered alkaline with ammonium hydrate, and finally precipitated with an ammoniacal solution of silver nitrate. The precipitate, consisting of the silver compounds of the xanthine bodies, is partially dried by spreading over porous porcelain plates; then dissolved in warm nitric acid of specific gravity of 1.1, to which a little urea has been added to prevent the formation of oxidation or nitro-products. The filtered acid solution, on cooling, gives a deposit of the silver salts of hypoxanthine, guanine, and adenine, which is filtered off and thoroughly washed. The filtrate contains any xanthine silver compound that may be present. The washed precipitate of the silver salts is suspended in water, decomposed with hydrogen sulphide, and the clear filtrate is concentrated on the water bath to a small volume. It is then saturated with ammonium hydrate and digested on the water bath for some time, whereby adenine and hypoxanthine go into solution, whilst the guanine remains undissolved. From the ammoniacal solution on partial concentration and subsequent cooling, the adenine crystal-

lizes out first, whereas the more soluble hypoxanthine remains in solution.

Another method for the separation of adenine from hypoxanthine is based upon the behavior of the nitrates of these bases in aqueous solution. From concentrated aqueous solutions of the nitrates, free hypoxanthine crystallizes out first, because the nitrate is decomposed; whereas, adenine, which is a stronger base, remains in combination with the acid, in solution.

Adenine, when crystallized from warm or impure solutions, is obtained either as an amorphous substance, or in the form of very small microscopic needles; from dilute cold solutions it separates in long, needle-shaped crystals containing three molecules of water. This water of crystallization is lost on exposure to the air or on heating to 53°, and the crystals become opaque. It is soluble in about 1086 parts of water at the ordinary temperature; more easily in hot water, from which, on cooling, it recrystallizes. The aqueous solution possesses a neutral reaction. The free base is insoluble in ether, chloroform, and alcohol; soluble in glacial acetic acid, and somewhat in hot alcohol. It dissolves readily in mineral acids, yielding well-crystallizable salts. The fixed alkalies dissolved it with ease, but on neutralization of the solution it is reprecipitated. In aqueous ammonium hydrate it is more readily soluble than guanine, and more difficultly soluble than hypoxanthine—a fact which is made use of to effect a separation from these bases. It is but slightly soluble in sodium carbonate.

Adenine can be heated to 278° without melting; at this temperature it becomes slightly yellow, and yields a white sublimate. It can be completely volatilized without decomposition, by heating on an oil-bath to 220°; the sublimate consists of pure, white, plumose needles of adenine, but at

250° partial decomposition occurs, and some hydrocyanic acid forms. When heated with potassium hydrate to 200° on an oil-bath, it yields a considerable quantity of potassium cyanide. Adenine is quite indifferent to the action of acids, alkalies, and even oxidizing agents. Thus, it may be boiled for hours with baryta, potash, or hydrochloric acid, without suffering decomposition. But when heated with dilute hydrochloric acid, or concentrated hydriodic acid, in a sealed tube at a temperature exceeding 100°, adenine is completely decomposed, with formation of carbonic acid and ammonia :

$$C_5H_5N_5+5H_2O+5O=5CO_2+5NH_3.$$

The free base, as well as benzoyl-adenine, is unaffected by the weak oxidizing action of potassium permanganate, but on stronger oxidation it is wholly destroyed. Bromine water produces in aqueous solutions of adenine an oily precipitate, which, on contact with potassium hydrate or ammonia, gives a beautiful red or violet color. Sodium amalgam and zinc chloride appear to have no action; but on boiling with zinc and hydrochloric acid it yields a very unstable reduction-product, which in the presence of oxygen first assumes a red color, and finally throws down a reddish-brown precipitate. This brown substance appears to be identical with azulmic acid, which has been known for a long time as a product of the polymerization of hydrocyanic acid.

When adenine is evaporated on the water-bath with dilute or fuming nitric acid, it gives a white residue which fails to give any coloration with sodium hydrate. Similarly, it does not give the so-called WEIDEL'S reaction (murexide test) on evaporation with chlorine water and exposure of the residue to an ammoniacal atmosphere. In this respect it resembles hypoxanthine, which, when pure, does not

answer to either of these tests. Another test for adenine, which, however, is given also by hypoxanthine but not by guanine and caffeine, is as follows: The substance to be tested is digested for half an hour with zinc and hydrochloric acid in a test-tube on the water-bath. If adenine is present, the solution will assume on standing, more rapidly on shaking, a ruby-red coloration, which later on turns into a brownish-red. This reaction depends upon the formation of a reduction product, which, owing to its unstable nature, is soon oxidized by the oxygen of the atmosphere into a brownish, amorphous substance, apparently identical with azulmic acid.

On treatment with nitrous acid, it is converted into hypoxanthine according to the equation:

$$C_5H_5N_5 + HNO_2 = C_5H_4N_4O + N_2 + H_2O.$$

This formation of hypoxanthine from adenine is analogous to STRECKER'S transformation of guanine into xanthine by a similar action of nitrous acid (see page 242). In both cases the change of a highly nitrogenized body into a less nitrogenized body is accomplished by replacing an NH group by O, or, more exactly, of an NH_2 group by OH. In fact, the change is identical with that seen in the conversion of primary amines into primary alcohols. Thus,

$$\underset{\text{ETHYLAMINE.}}{C_2H_5.NH_2} + HNO_2 = \underset{\text{ETHYL ALCOHOL.}}{C_2H_5OH} + N_2 + H_2O.$$

The ease with which adenine and guanine are reduced outside of the organism shows that similar changes may take place within the cell-nucleus proper. For we know that every cell is endowed with an enormous reducing power, and hence it is not difficult to see how the oxygen-free adenine can be readily converted into a body or bodies which greedily take up oxygen. We must, therefore, look

upon adenine and guanine not only as the antecedents of hypoxanthine and xanthine, but also as intermediate products which, when they form in the cell, may give rise to important chemical processes, especially those of a synthetic nature. It is highly probable that the study of the decomposition-products of nuclein will explain to us many of the metabolic changes in the organism, and throw additional light upon the migration of the amido group from the proteid molecule to the amido acids and urea derivatives. Thus, the formation of xanthine from guanine represents the conversion of a guanidine residue into a urea residue. A similar change is undoubtedly effected in the transformation of adenine into hypoxanthine.

Adenine unites with bases, acids, and salts. The salts of adenine with mineral acids can be recrystallized, thus differing from the corresponding salts of guanine and hypoxanthine, which are dissociated by the action of water. The solutions of the salts, however, possess an acid reaction.

The hydrochloride, $C_5H_5N_5.HCl+\frac{1}{2}H_2O$, forms colorless, transparent, strongly refracting crystals. One part of the anhydrous salt is soluble in 41.9 parts of cold water.

The nitrate, $C_5H_5N_5.HNO_3+\frac{1}{2}H_2O$, crystallizes from the aqueous solution in fine, stellate needles. One part of the dry salt dissolves in 110.6 parts of water.

The sulphate, $(C_5H_5N_5)_2.H_2SO_4+2H_2O$, can be obtained from the aqueous solution in two different crystalline forms. It is easily soluble in hot water, and at the ordinary temperature it is soluble in 153 parts of water.

The oxalate, $C_5H_5N_5.C_2H_2O_4+H_2O$, is obtained by dissolving adenine in hot, dilute, aqueous oxalic acid, from which solution, on cooling, it separates as a voluminous, difficultly soluble precipitate of roundish masses which are composed of long, delicate needles. The oxalates of guanine,

hypoxanthine, and xanthine are more easily soluble than that of adenine, and exhibit, moreover, a different appearance.

The platinochloride, $(C_5H_5N_5.HCl)_2PtCl_4$, crystallizes from dilute aqueous solution in small yellow needles. The concentrated aqueous solution of this salt, when boiled for some time, decomposes, with the separation of a clear, yellow powder, which is but slightly soluble in cold water, and has the composition $C_5H_5N_5.HCl.PtCl_4$.

The silver salt of adenine, $C_5H_4N_5Ag$, is formed when silver nitrate is added in molecular proportion to a boiling ammoniacal solution of adenine. An excess of silver nitrate produces, in the cold, the compound $C_5H_5N_5.Ag_2O$, which is converted slowly in the cold, immediately on warming, into the other salt according to the equation :

$$2C_5H_5N_5.Ag_2O = 2C_5H_4N_5Ag + Ag_2O + H_2O.$$

Both silver compounds are difficultly soluble in water and ammonia. Like hypoxanthine and guanine it forms another silver salt having the composition $C_5H_5N_5.AgNO_3$. It is obtained by dissolving the other silver compounds in hot nitric acid; and from this solution, on cooling, it separates in needle-shaped crystals which, however, are not permanent, but seem constantly to give off nitric acid.

Adenine, when treated with zinc and hydrochloric acid in the cold, forms a difficultly soluble crystalline double salt which has not been obtained in the pure state. This double salt is not obtained by direct treatment of adenine hydrochloride with zinc chloride.

One of the hydrogen atoms of adenine is capable of replacement by organic radicals. Thus, it forms crystalline methyl and ethyl compounds.

Acetyl-adenine, $C_5H_4N_5.CO.CH_3$, can be obtained by heating the anhydrous base with an excess of acetic

anhydride for some time, in an oil bath, at 130°. It crystallizes in small white scales which dissolve but slightly in cold water and in alcohol; more readily in hot water, in dilute acids and alkalies. Heated to 260° it becomes yellow but does not melt.

Benzoyl-adenine, $C_5H_4N_5.CO.C_6H_5$, is obtained by the action of benzoic anhydride, but not of benzoyl chloride, on adenine. It crystallizes from water in long, lustrous, thin needles which sometimes are grouped in bundles, and melt at 234°–235°. It is easily soluble in hot alcohol, from which it recrystallizes on cooling; also in dilute acids and in ammonia. With ammoniacal silver nitrate it gives a precipitate resembling that of adenine, but is more readily soluble in ammonia. This compound is quite stable, since it decomposes very slowly on boiling with hydrochloric acid; on protracted boiling with water it is changed into adenine and benzoic acid.

Picric acid unites with adenine to form an easily soluble compound. The aqueous solution of the base is precipitated by baryta water; alcoholic zinc chloride also yields a precipitate which is soluble in excess of ammonium hydrate. Mercuric chloride produces a precipitate, insoluble in hot water, but easily soluble in hydrochloric acid. Mercuric nitrate also gives a precipitate. Cadmium chloride yields a precipitate which dissolves on warming, reappears on cooling, and is soluble in ammonia. Basic lead acetate has no effect

Nothing definite is known in regard to the physiological action of adenine, except that when fed to dogs it appears to be eliminated as such, in part at least, by the urine.

Hypoxanthine, $C_5H_4N_4O$, sometimes also known as sarcine or sarkine, was discovered by Scherer (1850) in

splenic pulp, and in the muscles of the heart, and was named thus because it contains one atom of oxygen less than xanthine. It has since been obtained, usually accompanying adenine and guanine, from nearly all of the animal tissues and organs rich in nucleated cells, *i. e.*, in nuclein. It has been found in blood after death, but not in blood when flowing through the bloodvessels. SALOMON has recently shown it to be a normal constituent of urine; present, however, in an exceedingly minute quantity. In the blood and urine of leucocythæmic patients it occurs in increased quantity owing to the abnormally large number of nucleated white blood corpuscles in circulation (see page 228). BENCE JONES observed in the urine of a boy, who about three years before showed the symptoms of renal colic, a deposit of characteristic whetstone-like crystals resembling uric acid, but differing from the latter by dissolving readily on the application of heat, whilst from hydrochloric acid it crystallized in elongated six-sided plates. These crystals he considered to be those of xanthine, but SCHERER and others consider them to be hypoxanthine. It is therefore quite possible, though very rare, for this base to form a deposit in the urine and to be confounded in shape with uric acid. THUDICHUM has obtained it from the urine of persons sick with liver or kidney diseases.

Among other places it has been found in the brain, muscle, serum, marrow of bones, kidney, heart, spleen, liver, peripheral muscles; in the spawn of salmon (PICCARD), in the testicles of the bull (SALOMON), in the nuclein of pus and red corpuscles (KOSSEL), in developing eggs, and in putrefaction of albumen (SALOMON). It has also been found in the spores of lycopodium, and in the pollen of various plants, in seed of black pepper, in grass,

clover, oats, bran of wheat, larvæ of ants; in the juice of potato (SCHULZE); in certain wines (KAYSER); in the aqueous decoction of yeast of beer (SCHÜTZENBERGER); and also in the liquid in which yeast is grown (BECHAMP). DEMANT has shown it to be relatively abundant in the muscles of pigeons in a state of inanition, whilst in muscles of well-fed pigeons it is said to be entirely absent. SALOMON found hypoxanthine and xanthine in the cotyledons of lupine, as well as in the sprouts of malt; whilst REINKE and RODEWALD observed these two bases together with guanine in Æthalium septicum.

Hypoxanthine has not been extracted from the pancreas, where it seems to be replaced by guanine, or rather by adenine. It seems that hypoxanthine bears a relation to adenine similar to that which we see between glycocoll and glycocolic acid.

Hypoxanthine occurs frequently in plants together with the other members of this group, namely, adenine, guanine, and xanthine. The widely distributed character of these bases is due to the presence of a parent substance, viz., nuclein, the necessary constituent of all cells capable of development, which under the influence of acids, and probably likewise of ferments, decomposes into the above mentioned bases. They may, therefore, be considered as the first steps in the retrograde metamorphosis of all tissues, since they have their origin in nuclein, an important proteid substance. Recent advances in biological chemistry have shown that the undeveloped eggs of various insects and birds yield much less quantity of xanthine bodies (hypoxanthine, xanthine, etc.) on treatment with dilute acid than the partially developed eggs (TICHOMIROFF, KOSSEL). This is dependent upon the remarkable fact observed by KOSSEL that the nuclein of undeveloped

chicken eggs differs from the nuclein of cell nuclei and resembles that obtained from milk. For, while the nuclein from the cell nuclei decomposes into adenine, guanine, hypoxanthine, etc., that from undeveloped eggs and from milk yields no nitrogenous bases on treatment with acids. But as the egg develops, *i. e.*, the nucleated cells increase in number, this latter nuclein is gradually converted or gives way to the ordinary cell nuclein, and hence it is that the chick embryo yields guanine, hypoxanthine, and possibly adenine.

Unquestionably, the presence of hypoxanthine, etc., in developing cells is due to the presence of the nuclein molecule from which it is readily split off. In muscle, however, hypoxanthine and xanthine appear to exist preformed, and bear no relation to nuclein, since they are in the free condition, and can be extracted from the tissue by water. For an explanation of this peculiar fact, see adenine, page 229, and guanine, page 244.

According to the observations of SALOMON and CHITTENDEN, hypoxanthine is formed by the digestion of blood fibrin with gastric juice, pancreatic juice, or on heating with water or dilute acids. Egg albumen under the same conditions does not yield any hypoxanthine, except when treated with pancreatic juice. These observations require repetition, inasmuch as the fibrin used undoubtedly contained nuclein, which, as we now know, readily decomposes under those conditions into its characteristic nitrogenous bases. Be that as it may, it appears, however, to be one of the products formed by the decomposition and successive oxidation of proteid matter previous to the formation of uric acid and urea.

When a mixture of guanine, xanthine, and hypoxanthine is allowed to putrefy, the bases decompose and disappear in

the order named. Hypoxanthine resists bacterial action the longest, and this corresponds with its behavior to reagents.

Hypoxanthine can be readily obtained from a number of closely related substances. Thus, carnine, by the action of oxidizing agents, is converted into hypoxanthine (page 264). For this reason WEIDEL and SCHÜTZENBERGER regard hypoxanthine as derived from carnine, but this view is now entirely set aside by our present knowledge of the relation of this base to nuclein.

Again, it can be obtained from adenine (page 233) by the action of nitrous acid. The relation that hypoxanthine bears to uric acid is shown by the fact that the latter is converted by nascent hydrogen first into xanthine, and finally into hypoxanthine.

$$\underset{\text{URIC ACID.}}{C_5H_4N_4O_3} + 2H_2 = C_5H_4N_4O + 2H_2O.$$

This transformation of uric acid into hypoxanthine is of especial importance, since together with HORBACZEWSKI'S synthesis of uric acid, accomplished by acting on urea with either glycocoll or trichlorlactamide, it constitutes the last step in the complete synthesis of hypoxanthine from its elements.

Hypoxanthine has been hitherto regarded as a step lower than guanine in the series of nitrogenous products of regressive metamorphosis, and consequently was considered as derived from guanine. The investigations of KOSSEL, however, show that it arises not from guanine but from adenine. On the other hand, guanine is to be looked upon as the source of xanthine. It is probable that in the organism it is oxidized as soon as it is set free from the nuclein, forming successively xanthine, uric acid, urea, etc., and the small quantity present in the urine is all that has

escaped oxidation. When fed to dogs, it was observed that the amount of hypoxanthine present in the urine decreased, and even became less in amount than before the experiment; but, on the other hand, the amount of xanthine in the urine was found to have been increased above the normal. This shows that hypoxanthine in the body is oxidized probably first to xanthine, then into uric acid. According to ROBERT, hypoxanthine is a true muscle stimulant.

The fact that hypoxanthine is so widely distributed in the organism, and in much larger quantities than was formerly supposed, shows that it constitutes, together with the closely related bodies creatine, xanthine, guanine, etc., the normal antecedents of urea and uric acid. This view is furthermore strengthened since hypoxanthine is especially abundant in those organs which are most active in producing metabolic changes in the body, viz., the liver and spleen.

It may be prepared from the urine, according to the method given under paraxanthine (page 258); or from extract of meat, or from glandular organs, such as the liver, spleen, etc., by the process on page 230. Nuclein, on decomposition with acids, yields about one per cent. of this base.

Hypoxanthine is a white, colorless, crystalline powder, sometimes in part amorphous, soluble in about 300 parts of cold water. It is more easily soluble in boiling water (78 parts), and, on cooling, separates in the form of white, crystalline floccules, thus differing from xanthine, which is amorphous. The solubility in cold alcohol is very slight, about 1 to 1000. It dissolves in acids and alkalies without decomposition, and from solutions in the latter it can be precipitated by passing carbonic acid, or by the addition of acetic acid. The aqueous solution possesses a

neutral reaction. The free base can be heated up to 150° without suffering decomposition, but above this temperature it sublimes, and partially decomposes, with evolution of hydrocyanic acid. When heated with potassium hydrate to 200°, it yields ammonia and potassium cyanide. Heated with water to 200°, it decomposes into carbonic acid, formic acid, and ammonia, and in this respect it agrees with adenine (page 232).

When evaporated with an oxidizing agent, chlorine water or nitric acid, the residue is said to give on contact with ammonia vapors a rose-red color (WEIDEL, murexide test). KOSSEL, however, has shown that this is due to the presence of xanthine, and that pure hypoxanthine does not give either the murexide test or the xanthine reaction. According to STRECKER, concentrated nitric acid converts hypoxanthine into a nitro-compound, which in turn, by the action of a reducing agent, is changed into xanthine. This statement has not been confirmed either by FISCHER or by KOSSEL. It does not give a green color with sodium hydrate and chloride of lime—distinction from xanthine (page 251).

With acids it yields crystallizable compounds, and, like the amido acids, it forms compounds with bases, and also with metallic salts, such as silver nitrate and copper acetate.

The hydrochloride, $C_5H_4N_4O.HCl+H_2O$, crystallizes in needles, and, like the nitrate and sulphate, it is dissociated on contact with water. The nitrate forms thick prisms or roundish masses, readily soluble in water and ammonia. Platinum chloride forms a yellow, crystalline double salt, having the composition $C_5H_4N_4O.HCl.PtCl_4$.

Phosphomolybdic acid precipitates it from acid solution, and in general it gives the ordinary alkaloidal reactions.

It is not precipitated by ammoniacal basic lead acetate.

Copper acetate does not precipitate it in the cold, but does on boiling. This fact has been made use of in the isolation of hypoxanthine. Mercuric chloride, as well as mercuric nitrate, produces a flocculent precipitate.

Altogether, in its behavior to reagents, it resembles xanthine to a very considerable degree. The two can be separated, however, by the different solubilities of the hydrochlorides in water, and more especially of the silver salt in nitric acid. Silver nitrate produces, in an ammoniacal solution of these bases, a precipitate which is soluble in hot nitric acid, specific gravity 1.1; on cooling, the hypoxanthine silver compound, $C_5H_4N_4O.AgNO_3$, crystallizes readily in the form of tufts of microscopic needles or plates, whereas the xanthine compound separates very slowly. From the ammoniacal solution hypoxanthine is precipitated by silver nitrate as $C_5H_4N_4O.Ag_2O$, corresponding to the xanthine compound, $C_5H_4N_4O_2.Ag_2O$. Like adenine, it probably forms another silver compound in ammoniacal solution, having the composition $C_5H_3AgN_4O+H_2O$.

GUANINE, $C_5H_5N_5O$, was discovered, in 1844, by UNGER, as a constituent of guano, in which it is present in varying quantities according to the region from which the guano comes. Thus, the Peruvian guano is reported as containing the largest proportion of this base, and on that account this variety is employed when it is desired to prepare guanine. Since its discovery by UNGER, it has been met with in a very large number of tissues, both animal and vegetable; in the liver, pancreas, lungs, retina, and in the testicle substance of the bull; in the scales of the bleak, and in the swimming bladder of fish, as well as in the excrements of birds and insects. It is also found in the spawn and testicle of salmon, and SCHULZE and others have shown it to be

present in the young leaves of the plane-tree, of vine, etc., also in grass, clover, oats, as well as in the pollen of various plants. SCHÜTZENBERGER has isolated it, together with hypoxanthine, xanthine, and carnine, from yeast which had been allowed to stand in contact with water at near the body temperature. Pathologically, it occurs in the muscles, ligaments, and joints of swine suffering from the disease known as guanine-gout. Normally, guanine, like adenine, is present in muscle tissue only in traces. It has never been found in the urine, though xanthine has been mistaken for guanine by some.

As to the origin of this substance in the organism very little has been known up to within a few years, except so far as it has been shown to be, together with other members of this group, a transitory product in the retrograde metamorphosis of nitrogenous foods and tissues. In the case of the lower animals it is evidently the end-product of all change, inasmuch as it is excreted as such. Our knowledge as to the immediate origin of this and the other allied bases has lately been extended by the brilliant researches of KOSSEL, on the decomposition-products of nuclein, in which he has shown that this essential constituent of all nucleated cells, whether animal or vegetable, decomposes under the action of water or dilute acids into adenine, guanine, hypoxanthine, and xanthine. We know that the first two bases are readily converted by the action of nitrous acid into the other two; that is to say, an NH group in these bases is replaced by an atom of O—a change which it is not at all unlikely takes place in the tissues, perhaps in every cell nucleus. If this explanation is correct, then adenine and guanine are transition-products between the complex proteid molecule on the one hand, and hypoxanthine and xanthine on the other. These two, in turn, form the connecting link

to the last step in the regressive metamorphosis of the nitrogenous elements of the tissues, viz., the formation of uric acid and urea. We can thus trace a succession of cycles from the complex nuclein molecule, which is apparently indispensable to the functional activity of all reproductable cells, to the physiologically waste products urea and uric acid.

SCHULZE and BOSSHARD recently (1886) found in young vetch, clover, ergot, etc., a new base, to which they have given the name vernine. It has the formula $C_{16}H_{20}N_8O_8$, and is of especial interest at this point, since on heating with hydrochloric acid it apparently yields guanine. We have, therefore, at least two well-defined sources of guanine, the nucleins and vernine.

Neither adenine nor guanine occurs in normal muscle further than in mere traces, a fact which can only be explained on the ground that the muscle tissue is poor in nucleated cells, and hence in nuclein. Just as the muscle cell has become morphologically differentiated from the typical cell, it may be looked upon also as having undergone a concomitant chemical differentiation, inasmuch as we no longer find the phosphoric acid, xanthine, and hypoxanthine in the same chemical combination as they occur in the original cell. The phosphoric acid, instead of existing as a part of an organic compound, is present in the muscle tissue as a salt; similarly the hypoxanthine and xanthine occur in the free condition, extractable by water, and no longer in combination with other groups of atoms constituting a part of a more complex molecule—nuclein.

Guanine and creatine apparently mutually replace one another. Thus, in the muscle, as just stated, guanine occurs only in traces, whereas creatine is especially abundant. This may find its explanation in the fact that both are sub-

stituted guanidines. Creatine is regarded by HOPPE-SEYLER as an intermediate product in the formation of urea, and a similar rôle, it will be remembered, belongs to guanine.

In the decomposition of nuclein-containing substances, such as yeast, liver, spleen, etc., by dilute acids, neither adenine nor guanine is found alone, but they are always accompanied by hypoxanthine, and usually by a very small quantity of xanthine.

Guanine may be readily prepared from Peruvian guano by boiling it repeatedly with milk of lime until the liquid becomes colorless. The residue, consisting largely of uric acid and guanine, is boiled with a solution of sodium carbonate, filtered, and the filtrate, after the addition of sodium acetate, is strongly acidulated with hydrochloric acid. This precipitates the guanine, together with some uric acid. The precipitate is dissolved in boiling hydrochloric acid, and the guanine then thrown out of solution by the addition of ammonium hydrate. Guanine is also obtained in the decomposition of nuclein with dilute acids, and can, therefore, be prepared from such cellular organs as the spleen, pancreas, etc., according to the method given on page 230.

The free base forms a white, amorphous powder, insoluble in water, alcohol, ether, and ammonium hydrate; easily soluble in mineral acids, fixed alkalies, and in excess of concentrated ammonium hydrate. It can be heated to above 200° without undergoing decomposition. When evaporated with strong nitric acid it gives a yellow residue, and this on the addition of sodium hydrate assumes a red color, which on heating becomes purple. This is the so-called xanthine reaction, and is supposed to be due to the formation of xanthine and a nitro product. It is given

best by guanine, then by xanthine, and is not given by either hypoxanthine or adenine.

Nitrous acid converts it directly into xanthine. Thus:

$$C_5H_5N_5O + HNO_2 = C_5H_4N_4O_2 + N_2 + H_2O.$$

This reaction is identical with that of adenine, whereby hypoxanthine is formed (see page 233). On oxidation with potassium permanganate it yields urea, oxalic acid, and oxyguanine. By hydrochloric acid and potassium chlorate it is oxidized to carbonic acid, guanidine, and parabanic acid, according to the equation:

$$C_5H_5N_5O + H_2O + 3O = \underset{\text{Parabanic Acid.}}{\begin{matrix} CO{-}NH \\ | \quad\quad \diagdown CO \\ CO{-}NH \diagup \end{matrix}} + \underset{\text{Guanidine.}}{\begin{matrix} H_2N \diagdown \\ H_2N \diagup \end{matrix} C{=}NH} + CO_2.$$

According to Strecker, a small amount of xanthine is formed in this reaction, and it is quite possible that this base is also formed on oxidation with nitric acid.

Guanine combines with acids, bases, and salts. It unites with bases to form crystalline compounds; and with one or two equivalents of acids it also yields crystallizable salts. Thus, with hydrochloric acid it forms the two salts, $C_5H_5N_5O.(HCl)_2$ and $C_5H_5N_5O.HCl + H_2O$. Similar combinations can be obtained with nitric acid. The sulphate, $(C_5H_5N_5O)_2H_2SO_4$, crystallizes in long needles, and, like the other salts, is decomposable by water. The platinochloride, $(C_5H_5N_5O.HCl)_2PtCl_4 + 2H_2O$, is readily obtained in a crystalline condition. The silver compound is soluble in hot nitric acid, and on cooling recrystallizes in fine, needle-shaped crystals having the composition $C_5H_5N_5O.AgNO_3$.

The solutions of the hydrochloride are precipitated by mercuric chloride and nitrate, potassium chromate, potassium ferricyanide, and by picric acid. Basic lead acetate

gives a precipitate only on addition of ammonium hydrate. The reaction with picric acid (CAPRANICA) is said to be very characteristic, and a means of distinguishing this base from xanthine and hypoxanthine. It is best obtained by adding a cold, saturated solution of picric acid to the warm, acidulated solution of guanine, when a light, crystalline precipitate forms. Under the microscope it appears in pencil-shaped, fern-like tufts of fine, orange-yellow needles.

XANTHINE, $C_5H_4N_4O_2$, is also very widely distributed in the organism, and has been met with in almost all the tissues and liquids of the animal economy. Together with hypoxanthine, guanine, and possibly adenine, it occurs in many plants, among which may be mentioned lupine, æthalium, sprouts of malt, etc. It was first discovered by MARCET (1819) in a urinary calculus, and since then has been frequently found as the only or chief constituent of many calculi. UNGER and PHIPSON have extracted it from guano, whilst SALOMON has shown it to be one of the products formed in the pancreatic digestion of fibrin. SCHÜTZENBERGER found it together with carnine and hypoxanthine in the liquors from yeast. It is a normal constituent of the urine, but is present only in extremely minute quantities. During the use of sulphur-baths or after the thorough application of sulphur salves the quantity of xanthine in the urine is considerably increased. It is likewise more abundant in the urine of leucocythæmic patients, for the reasons already given on page 228. BAGINSKI holds that the amount of xanthine normally present in the urine may be increased tenfold in the case of acute nephritis. BENCE JONES observed in the urine of a child sick with renal colic, a deposit of crystals which he considered to be xanthine, but other observers are inclined

to regard the crystals rather as hypoxanthine. VAUGHAN has reported the presence of xanthine in deposits from the urine of patients with enlarged spleen.

Xanthine may be prepared synthetically in several ways. Thus, it may be obtained by the reduction of uric acid by means of sodium amalgam, according to the equation :

$$\underset{\text{URIC ACID.}}{C_5H_4N_4O_3} + H_2 = \underset{\text{XANTHINE.}}{C_5H_4N_4O_2} + H_2O.$$

Now that uric acid has been prepared synthetically, this forms the final step in the complete synthesis of xanthine. By further action of nascent hydrogen the xanthine in turn is converted into hypoxanthine. It is, therefore, evident that these bodies form a continuous oxidation series with uric acid as the final product. Although this change is unquestionably the one which goes on in the animal economy, yet all attempts to reproduce it in the laboratory by oxidation with potassium permanganate or nitric acid have apparently yielded only negative results. Again, xanthine may be prepared from guanine by oxidation with nitrous acid. The change may be represented by this equation :

$$\underset{\text{GUANINE.}}{C_5H_5N_5O} + HNO_2 = \underset{\text{XANTHINE.}}{C_5H_4N_4O_2} + N_2 + H_2O.$$

This reaction, first described by STRECKER (1858), corresponds exactly to the one by which KOSSEL has transformed adenine into hypoxanthine (see page 233).

GAUTIER, starting out on the hypothesis that xanthine is a polymerization-product of hydrocyanic acid, has endeavored to prepare it directly from this compound. Indeed, he claims to have succeeded in effecting the synthesis of not only xanthine, but also its homologue, by simply heating hydrocyanic acid in a sealed tube with

water and a little acetic acid; the latter being added to neutralize any ammonia that might form. He expresses the reaction as follows:

$$11HCN + 4H_2O = \underset{\text{Xanthine.}}{C_5H_4N_4O_2} + \underset{\text{Methyl-xanthine.}}{C_6H_6N_4O_2} + 3NH_3.$$

Nearly all of the methods that have been employed for the preparation of xanthine are based upon its precipitation as the insoluble silver compound. From the urine it can be isolated according to the method given under paraxanthine, on page 258. It may also be obtained from the urine by Hofmeister's method. The urine, acidulated with hydrochloric acid, is precipitated with phosphotungstic acid; the precipitate is decomposed by warming with baryta, filtered, and the filtrate is freed from barium by the cautious addition of sulphuric acid. The solution is then made alkaline with ammonium hydrate, any traces of phosphates that appear are filtered off, and finally it is precipitated by addition of ammoniacal silver nitrate. The precipitate which forms consists of the silver compounds of the xanthine bodies, and is purified by dissolving in hot nitric acid, as given on page 230. Xanthine has been shown to be formed at the same time with guanine, adenine, and hypoxanthine, in the decomposition of nuclein by means of dilute acids. It may, therefore, be prepared from cellular organs according to the method given under adenine.

Xanthine is a white, granular, amorphous body, and is deposited from hot aqueous solution on cooling in colorless floccules, or as a fine powder, which, under the microscope, is seen to consist of rounded granules. When occurring in calculi, it forms compact, moderately hard, yellow or brown fragments, which, on being rubbed with the finger-nail, assume a wax-like appearance. It is difficultly soluble in cold water (about 14,000 parts), alcohol, and ether; some-

what more soluble in boiling water (about 1200 parts). It is soluble in alkalies and alkali carbonates, not bicarbonate, and from these solutions it is precipitated on neutralization with acids, or by passing carbonic acid. In warm ammonia it dissolves more readily than does uric acid or guanine, and on cooling the ammonium compound recrystallizes. It acts as a weak base, and as a weak acid; with salts of the heavy metals it forms difficultly soluble or insoluble compounds. Its basic properties, however, are weaker than those of hypoxanthine or guanine.

When xanthine is evaporated with nitric acid it leaves a lemon-yellow residue (hence its name), which is not changed by ammonium hydrate—distinction from uric acid—but with potassium hydrate becomes yellowish-red, on heating purple-red. When added to a mixture of bleaching powder and sodium hydrate in a watch-glass the solution becomes covered by a dark-green scum, which changes to a brown, and soon disappears—distinction from hypoxanthine.

By means of a very interesting synthetic reaction, xanthine may be converted into theobromine, the active constituent of Theobroma cacao. Thus, the xanthine is dissolved in a sufficient quantity of sodium hydrate, necessary to form the neutral compound $C_5H_2Na_2N_4O_2$, and this product, when treated with boiling acetate of lead, yields a white precipitate of lead xanthine, $C_5H_2PbN_4O_2$. This is dried at 130°, then heated for twelve hours at 100° with methyl iodide, when the dimethyl derivative, $C_5H_2(CH_3)_2N_4O_2$, is formed. This compound is identical with the natural theobromine, and by a similar treatment is converted into trimethyl-xanthine or caffeine. The relation of xanthine to theine (caffeine) is shown in the fact that it exists together with hypoxanthine, adenine, and possibly guanine, in fresh tea-leaves. It is, therefore, clear that by starting from

guanine of guano we can produce successively xanthine, dimethyl xanthine, and trimethyl xanthine, the last two compounds being identical with the alkaloids of theobroma and of coffee.

Nascent hydrogen converts this base into hypoxanthine, but the reverse operation, the oxidation of hypoxanthine into xanthine, has been questioned of late by KOSSEL and others. On heating, a small portion volatilizes; the greater part decomposes into ammonium carbonate, cyanogen, and hydrocyanic acid. Heated to 200° with hydrochloric acid, it decomposes with the formation of ammonia, carbonic acid, formic acid, and glycocoll (E. SCHMIDT). When bromine is allowed to act on xanthine, there is formed a substitution compound, having the formula $C_5H_3BrN_4O_2$. With potassium chlorate and hydrochloric acid it yields alloxan and urea.

Xanthine is a weak base, which dissolves in acids with the formation of salts.

The hydrochloride, $C_5H_4N_4O_2.HCl$, is difficultly soluble in water, more so than the corresponding salt of hypoxanthine, from which it is deposited in glistening six-sided plates, often forming aggregations. Its solution does not precipitate platinum chloride. The nitrate forms fine yellow crystals.

The sulphate, $C_5H_4N_4O_2.H_2SO_4 + H_2O$, crystallizes in microscopic glistening rhombic plates, decomposable by water.

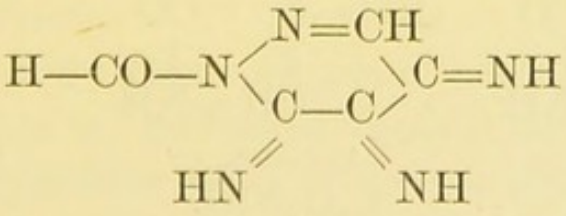
With baryta water, xanthine forms the difficultly soluble compound $C_5H_4N_4O_2.Ba(OH)_2$, which corresponds to the hypoxanthine salt $C_5H_4N_4O.Ba(OH)_2$, and to that of guanine.

From ammoniacal solution, silver nitrate precipitates the compound $C_5H_4N_4O_2.Ag_2O$, which is insoluble in ammonia, but soluble in hot nitric acid. From the nitric acid solu-

tion, on long standing, there separates the compound $C_5H_4N_4O_2.AgNO_3$, which, on contact with water, decomposes, giving off nitric acid. The ammoniacal solution is also precipitated by lead acetate—separation from hypoxanthine—also by calcium and zinc chlorides. Cupric acetate gives a precipitate only on boiling. The aqueous solution is not precipitated by lead acetate, but is by phosphomolybdic acid, phosphotungstic acid, by mercurous and mercuric salts. Picric acid gives an easily soluble compound, which resembles that of hypoxanthine, but differs from that of guanine.

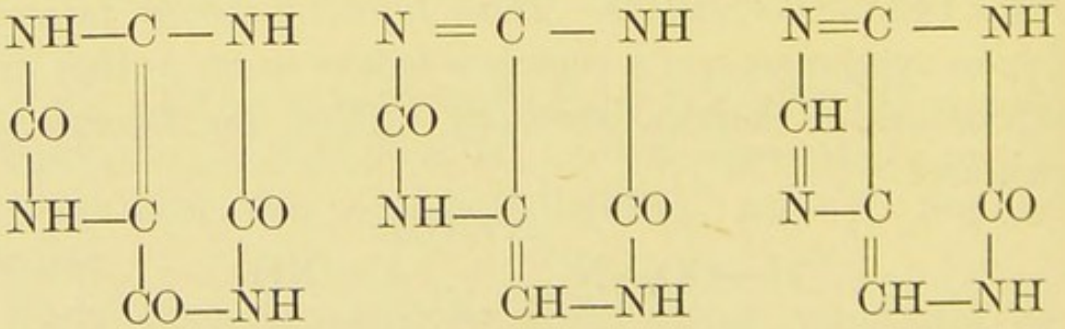
As to the physiological relation of xanthine very little need be said. It bears the same relation to guanine that hypoxanthine does to adenine, and, like the latter, is to be looked upon as an intermediate compound, a step lower than guanine, and nearer the limit of oxidation—uric acid. It is quite probable that in the body it is oxidized about as rapidly as it is formed. Like hypoxanthine, it is to be regarded as a true muscle stimulant, especially of the heart. (Baginski.)

In closing the description of the preceding bodies it may be well to present briefly our present knowledge as to their constitution. Gautier, starting out with the idea that they are polymerization-products of hydrocyanic acid, has deduced theoretically cyclic formulæ, recalling the hexagon of the benzole derivatives. These formulæ, though formidable in appearance, are a complete failure so far as they are expressions of chemical reactions. Thus, the formula of guanine:



fails to show either a urea or a guanidine residue, and yet it is a well-known fact that guanine on oxidation yields parabanic acid and guanidine (page 247). In a similar manner, his xanthine formula fails to show up the urea residues which we know to be present.

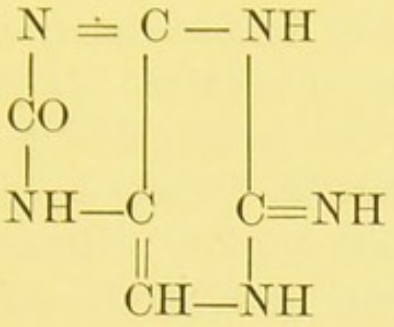
HORBACZEWSKI'S synthesis of uric acid has thrown considerable light upon the constitution of these bases. As a consequence of his method of synthesis uric acid was shown to possess the structural formula given below. E. FISCHER has found, as a result of experimental work, the constitution of xanthine to be expressed by the subjoined formula. We know that uric acid on treatment with nascent hydrogen is converted into xanthine, then into hypoxanthine. It follows, therefore, that a relation exists between hypoxanthine and xanthine similar to that between xanthine and uric acid. The formula of hypoxanthine, as deduced from this relation, and given below, probably represents its constitution quite closely. It is possible, however, that the CH and CO groups will be found to occupy the reverse position which they are given in this formula, in which case corresponding changes must be made in the formulæ of guanine and adenine. The latter two are based upon the relation which these bodies bear to xanthine and hypoxanthine, and cannot be said to be the result of direct experimental evidence.



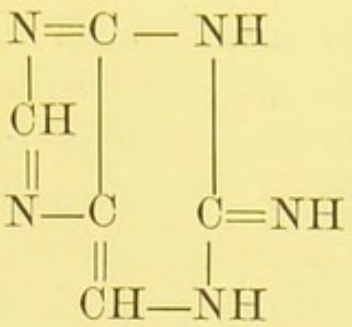
URIC ACID. $C_5H_4N_4O_3$

XANTHINE. $C_5H_4N_4O_2$

HYPOXANTHINE. $C_5H_4N_4O$



GUANINE.
$C_5H_5N_5O$



ADENINE.
$C_5H_5N_5$.

HETEROXANTHINE, $C_6H_6N_4O_2$, is a new base which was isolated from the urine in 1884 by SALOMON. In its composition it is methyl-xanthine, and is intermediate between xanthine and paraxanthine or dimethyl-xanthine. It occurs in the urine of man and of the dog in about the same amount as paraxanthine, and the method for its isolation will be found under the description of that base. It is a remarkable fact that this base occurs in dog's urine unaccompanied by paraxanthine, and the same seems to hold true for the urine of leucocythæmic persons. SALOMON examined the liver and muscles of a dog, but was unable to obtain any heteroxanthine or paraxanthine, and the total amount of xanthine bodies present was about normal. Hence, he is inclined to think that these two bases may possibly have their origin in the kidney. Unlike the other xanthine bodies, heteroxanthine has not as yet been isolated from plants, meat extract, or guano. The amount of xanthine bodies present in the urine is unaffected by phosphorus poisoning. Neither this base nor paraxanthine has been found in bull's testicles; xanthine is also absent, and only hypoxanthine and guanine were found to be present.

Heteroxanthine forms a white amorphous powder which sometimes on prolonged contact with water forms microscopic crystalline tufts. It is very difficultly soluble

in cold water; much more easily in hot water, and the solution thus obtained is neutral in reaction. It is easily soluble in ammonium hydrate, but is insoluble in alcohol and ether. When heated it volatilizes without melting and at the same time gives off a small quantity of hydrocyanic acid. On evaporation with nitric acid on the water bath (xanthine reaction) it remains as a pure white residue, which on contact with sodium hydrate develops only a trace of reddish coloration or none at all. WEIDEL'S test (page 264) produces a splendid red color which becomes blue on the addition of sodium hydrate. Simple evaporation with chlorine water gives a similar, though not so strong a color reaction.

Silver nitrate produces in ammoniacal, as well as in nitric acid solutions, a precipitate which dissolves on warming readily in even very dilute nitric acid; from this solution, if not too concentrated, the heteroxanthine silver nitrate compound crystallizes in well-formed plate-like prismatic crystals. Copper acetate produces in the cold, in solutions of heteroxanthine, a clear-green precipitate. It is also precipitated by phosphotungstic acid, and by ammoniacal basic lead acetate. Picric acid does not give a yellow colored precipitate in solutions of the hydrochloride. Mercuric chloride readily precipitates heteroxanthine in the form of a grayish-yellow compound, which on standing twelve to twenty-four hours becomes converted into pure white crystalline aggregations. This mercuric compound can be converted directly into the corresponding silver compound by the addition of silver nitrate and ammonia, as described under paraxanthine.

The hydrochloride is characterized by its rather difficult solubility and ready crystallization (a distinction from the paraxanthine salt). The salt forms large colorless tufts

of crystals, which on contact with water soon lose their transparency and become opaque; gradually their crystalline form disappears, till finally they completely decompose with the formation of heteroxanthine. This decomposition is hastened by warming, either with or without addition of ammonia. Platinum chloride produces in the hydrochloric acid solution a precipitate of a crystalline double salt.

This base resembles paraxanthine in its property of yielding a difficultly soluble precipitate with the fixed alkali. This reaction is best brought about by dissolving the heteroxanthine hydrochloride in warm dilute sodium hydrate, when, on cooling, the corresponding sodium salt will crystallize out in oblique angle plates. These crystals dissolve easily in water, and on neutralization of the solution with an acid a dense pulverulent precipitate of heteroxanthine forms. It can thus be distinguished from paraxanthine, the sodium compound of which, on similar treatment, yields the characteristic crystalline form of the free base. This sodium reaction, therefore, distinguishes it at once from xanthine, hypoxanthine, guanine, and paraxanthine. It differs from the latter, as has already been indicated, in the solubility and amorphous character of the free base; in the behavior of the hydrochloride and the sodium compound, and in the not giving a precipitate with picric acid, nor the characteristic odor given by paraxanthine on heating.

In its composition, heteroxanthine is, as has already been stated, methyl-xanthine and probably is related to if not identical with an isomeric body obtained synthetically by GAUTIER (see page 249). The fact nevertheless remains, that in the urine we have normally a homologous series of xanthine bodies, namely, xanthine, heteroxanthine, and paraxanthine.

PARAXANTHINE, $C_7H_8N_4O_2$, was isolated in 1883 by SALOMON, who has since shown it to be a constituent of normal urine, although present in exceedingly minute quantity. Thus from 1200 litres of urine, only 1.2 grams (0.0001 per cent.) of this substance were obtained. It has not been found in the urine of dogs or in that of leucocythæmic patients. THUDICHUM was the first to isolate paraxanthine from the urine, and he named it urotheobromine (1879).

The method employed for the isolation of this base is, with a slight modification, that of E. SALKOWSKI, as originally proposed for the preparation of the xanthine bases from urine. The urine in portions of 25 to 50 litres is made alkaline with ammonium hydrate and allowed to stand twenty-four hours. The clear supernatant fluid is decanted from the precipitate of phosphates and treated with silver nitrate (0.5 to 0.6 gram per litre). The grayish precipitate of xanthine compounds which forms is transferred to a filter and washed with water till free from chlorides; it is then suspended in water and decomposed with a current of hydrogen sulphide. The liquid is filtered by decantation and the filtrate is evaporated to dryness; the residue is extracted with three per cent. sulphuric acid to remove uric acid; the solution thus obtained, after it has been rendered alkaline with ammonia, is precipitated by silver nitrate.

A better procedure is to concentrate the filtrate directly over the flame or on the water bath, till the uric acid begins to crystallize out. It is then filtered, and the filtrate, after diluting somewhat with water, is rendered alkaline with ammonium hydrate in order to precipitate any remaining uric acid and phosphates. The whole is allowed to stand one or two days, then filtered, and the filtrate again pre-

cipitated with silver nitrate. The thoroughly washed precipitate of the xanthine compounds now obtained, free from uric acid, is dissolved in as little as possible of hot nitric acid of specific gravity 1.1, to which a little urea has been added, and the clear solution is set aside for twenty-four hours. The silver salt of hypoxanthine crystallizes from the solution and is filtered off. It can be purified by repeated recrystallization from hot nitric acid containing a little urea, then decomposed with hydrogen sulphide, and the filtrate, rendered alkaline with ammonium hydrate, is concentrated to a small volume. On standing, pure hypoxanthine crystallizes out. The filtrate from the silver salt of hypoxanthine on being rendered alkaline with ammonium hydrate gives a precipitate which formerly was regarded as consisting entirely of the xanthine silver compound, but which, from the investigations of SALOMON, has been shown to be a mixture of the salts of xanthine, paraxanthine, and heteroxanthine.

The separation of these bases is effected by the solubility of the free bases in ammonium hydrate. For this purpose the precipitate of the mixed silver salts is decomposed with hydrogen sulphide, and the filtrate is rendered ammoniacal to remove traces of phosphates and oxalates, and moderately concentrated. After standing twenty-four hours, heteroxanthine crystallizes out, partly in finely formed sheaves and tufts of needles, partly in radially striated masses. The fluid is decanted from the crust of heteroxanthine which forms in the bottom of the beaker and after being concentrated somewhat is again allowed to stand. In this way a second crop is obtained, and this is repeated till finally the separated masses scarcely give a precipitate with sodium hydrate. All the heteroxanthine is now united and dissolved in a little hot water by the aid of sodium

hydrate. After twenty-four hours the greater part of the heteroxanthine crystallizes out in bunches of crystals of sodium heteroxanthine, whilst a small part together with any traces of xanthine remains in solution. The crystalline mass is dried by pressure, dissolved in a little water, and the solution neutralized by addition of hydrochloric acid, when the heteroxanthine separates as a pulverulent precipitate. To remove any traces of paraxanthine, dissolve in hydrochloric acid; on standing forty-eight hours the heteroxanthine salt separates, whilst the easily soluble salt of paraxanthine remains in solution. To obtain the pure free heteroxanthine, the hydrochloric salt is evaporated with ammonium hydrate; the well-washed residue of heteroxanthine is then dissolved in dilute ammonia, the solution filtered, evaporated slowly, and the precipitate which forms is finally washed with alcohol and ether.

The original ammoniacal mother-liquors of heteroxanthine yield on further concentration amorphous floccules of xanthine, which are removed by filtration; and from the filtrate, when concentrated still more, paraxanthine crystallizes out.

Paraxanthine is obtained in colorless, glassy, generally six-sided plates, which are arranged in tufts or rosettes. From very concentrated aqueous solutions it crystallizes in long, colorless, interwoven needles, which on drying exhibit the silky lustre of tyrosin. The crystals belong to the monoclinic system, and do not contain any water of crystallization. It can be heated to 250° without melting or suffering any decomposition, but when heated more strongly it gives off white vapors which possess a distinct iso-nitril odor, at the same time it carbonizes and takes fire. When evaporated with concentrated nitric acid, as in the ordinary xanthine test, it gives only a slight yellow residue. On the other hand, WEIDEL'S test, evaporation with chlorine

water containing a trace of nitric acid, and then placing the dry residue into an ammoniacal atmosphere under a bell-jar, gives a beautiful rose-red color.

It is difficultly soluble in cold water (though more easily than xanthine); somewhat more readily soluble in hot water, and insoluble in ether and alcohol. It is soluble in ammonium hydrate, hydrochloric acid, and nitric acid. Its solutions react neutral.

Silver nitrate produces in nitric acid, as well as in ammoniacal solutions, a flocculent or gelatinous precipitate, which in concentrated solutions forms an almost perfect jelly-like mass. This silver precipitate is soluble in warm nitric acid, from which on cooling it separates in white crystalline tufts possessing a silky lustre. On decomposition with hydrogen sulphide the silver salt yields pure paraxanthine. Picric acid produces in the hydrochloric acid solution a precipitate consisting of densely felted yellow crystalline spangles.

It is also precipitated by phosphotungstic acid and copper acetate; mercuric chloride when added in excess gives a precipitate composed of a mass of colorless prisms, which are rather difficultly soluble in cold water; easily in hot water. The crystals of paraxanthine mercuric chloride when moderately heated become opaque from loss of water of crystallization; at a higher temperature they melt, undergoing at the same time partial decomposition, and on strong heating they evolve disagreeable nauseating vapors. The aqueous solution of this mercuric double salt gives with silver nitrate an abundant precipitate of silver chloride, which disappears on the addition of ammonium hydrate and is replaced by the flocculent gelatinous precipitate of silver paraxanthine. The hydrochloric acid solution of paraxanthine crystallizes with difficulty even when strongly concentrated, and on the addition of platinum chloride it

yields a well-crystallizable orange colored paraxanthine platinochloride. It is not precipitated by basic lead acetate nor by mercuric nitrate.

In its behavior to the xanthine test this base resembles hypoxanthine, whereas in giving WEIDEL'S reaction it approaches xanthine. Finally, it coincides with guanine by yielding a precipitate with picric acid. Although it thus agrees in some of its reactions with all three of these xanthine bodies, it can, however, be easily distinguished from them by its behavior with the fixed alkalies. Sodium or potassium hydrate dissolves these bases and holds them in solution, but when added to concentrated paraxanthine solution the alkali produces a precipitate of long, glittering, crystalline spangles, which under the microscope are seen to consist of delicate rectangular, often longitudinally striated, plates which are either isolated or united in tufts. Besides these crystals there are also present hexagonal plates resembling cystin. The crystals are soluble in a little water, or on warming, but precipitate again on cooling. Paraxanthine, however, shares with heteroxanthine the property of forming a difficultly soluble compound with the fixed alkalies, but can be distinguished from the latter by neutralizing with an acid the solution of the sodium or potassium compound, when, in the case of paraxanthine, there will be obtained a precipitate of the characteristic crystals of that base; whereas heteroxanthine is obtained on similar treatment as a dense pulverulent precipitate.

It is interesting to observe that paraxanthine is isomeric with theobromine, and also with a body recently described by FISCHER as dioxy-dimethyl-purpurine. In its composition it is, therefore, a dimethyl-xanthine.

CARNINE, $C_7H_8N_4O_3$, was isolated in 1871 from American meat-extract by WEIDEL, but has not been obtained

from muscle-tissue itself. It has also been obtained from yeast liquors by SCHÜTZENBERGER, and from urine by POUCHET. It can be separated from the meat extract, of which it forms about one per cent., by the following method originally employed by WEIDEL. The extract is dissolved in six or seven parts of warm water, then concentrated baryta water is added, avoiding however an excess. The filtrate is precipitated by basic lead acetate. The precipitate is collected, thoroughly washed and pressed, and finally it is repeatedly extracted with a large quantity of boiling water. The carnine lead salt is thus dissolved out, the filtrate, after removal of the lead by hydrogen sulphide, is evaporated to a small volume. The concentrated solution thus obtained is treated with silver nitrate, which gives a precipitate of silver chloride and of the silver salt of carnine. By treatment with ammonium hydrate the silver chloride can be completely removed from the precipitate, whereas the silver compound of carnine is insoluble in that reagent. To obtain pure carnine the silver salt is decomposed with hydrogen sulphide, and the filtrate after purification by bone-black is evaporated to crystallization.

Carnine forms white crystalline masses, which on drying become loose and chalk-like. It is very difficultly soluble in cold water, easily and completely in boiling water, and recrystallizes on cooling. It is insoluble in alcohol and ether. The taste is decidedly bitter, and the reaction is neutral. The base is not precipitated by neutral lead acetate, but is precipitated by the basic salt as a flocculent white precipitate, soluble in boiling water. On heating, carnine decomposes and takes fire, and at the same time gives off a peculiar odor. It crystallizes with one molecule of water, which it loses at 100°–110°.

The hydrochloride, $C_7H_8N_4O_3.HCl$, is crystalline, and decomposes on heating with concentrated hydrochloric acid.

The platinochloride, $C_7H_8N_4O_3.HCl.PtCl_4$, forms a fine sandy, gold-yellow powder.

With silver nitrate, carnine unites to form a white flocculent precipitate, insoluble in nitric acid or in ammonium hydrate. Its formula corresponds to $2(C_7H_7AgN_4O_3)+AgNO_3$.

Carnine is not affected by prolonged boiling with concentrated barium hydrate. Bromine water decomposes it with the evolution of gas and the formation of hypoxanthine. This change takes place according to the following equation :

$$C_7H_8N_4O_3+2Br=C_5H_4N_4O.HBr+CH_3Br+CO_2.$$

A similar decomposition into hypoxanthine is brought about by the action of nitric acid, though in this case oxalic acid and a yellow body are formed. When carnine is evaporated with chlorine water containing a little nitric acid, the residue, on contact with ammonia, gives a rose-red color (murexide test). This is due, according to WEIDEL, to the formation of hypoxanthine, but it has since been shown that the latter base does not give this reaction, and hence it is due to the production of xanthine, or some similar body.

The physiological action of carnine has been examined somewhat by BRÜCKE, and according to him it is not very poisonous. The only effect observed, when taken internally, was a fluctuation in the rate of the heart-beat, though even this was by no means definite in its nature.

A BASE, $C_4H_5N_5O$, was obtained by GAUTIER from fresh muscle tissue of beef, according to the method given

on page 269, and on account of a resemblance in some of its properties with xanthine, he named it pseudoxanthine. This name is very inappropriate, not only because it differs so much in its empirical formula from that of xanthine, $C_5H_4N_4O_2$, but also because the term pseudoxanthine has already been applied by SCHULTZEN and FILEHNE to a body isomeric with xanthine, which was obtained by the action of sulphuric acid on uric acid.

The free base forms a light-yellow powder, slightly soluble in cold water, soluble in weak alkali and in hydrochloric acid. The hydrochloride is very soluble, and it forms stellate prisms with curved faces, which resemble the corresponding salt of hypoxanthine, and to some extent, also, the whetstone-shaped crystals of uric acid.

Like xanthine, its aqueous solution is precipitated in the cold by mercuric chloride, silver nitrate, and by ammoniacal lead acetate, but not by normal lead acetate. On evaporation with nitric acid, the residue gives, on contact with potassium hydrate, as in the case of xanthine, a beautiful orange-red coloration (xanthine reaction). It differs from xanthine, not only in its empirical composition, but also in its greater solubility, and in its crystalline form. It is possible that this base, on account of its great resemblance to xanthine, may have been mistaken, at different times, for that compound.

SPERMINE, C_2H_5N, is the basic substance obtained by SCHREINER (1878) from semen, calf's heart, calf's liver, bull's testicles, and also from the surface of anatomical specimens kept under alcohol. Previous to this, however, it had been known for a long time under the name of "CHARCOT-NEUMANN crystals," which are the phosphate of spermine. These peculiarly shaped crystals have been

found in the sputa of a case of emphysema with catarrh, in the bronchial discharges in acute bronchitis, as well as in sputa of chronic bronchitis, in the blood, spleen, etc., of leucocythæmics and anæmics, and in the normal marrow of human bones, as well as in human semen. Altogether it seems to have a very wide distribution, especially in certain diseases, as in leucocythæmia.

It can be prepared from fresh human semen in the following manner: The semen is washed out of linen by a little warm water, evaporated to dryness, boiled with alcohol, and the insoluble portion is allowed to subside by standing some hours. The precipitate is filtered off, washed, and dried at 100°. This residue, containing the spermine phosphate, is triturated, and then extracted with warm ammoniacal water. From this solution, on slow evaporation, the phosphate crystallizes in its peculiar-shaped crystals.

The free base is obtained, on decomposing the phosphate with baryta and evaporating the filtrate, as a colorless liquid, which, on cooling, crystallizes. From alcohol it crystallizes in wavellite-shaped crystals, which readily absorb water and carbonic acid from the atmosphere. They are readily soluble in water and in absolute alcohol, almost insoluble in ether, and possess a strongly alkaline reaction. When heated with platinum it gives off thick, white fumes, and a weak ammoniacal odor. The aqueous solution of the base is precipitated by phosphomolybdic and phosphotungstic acids, tannic acid, gold and platinum chlorides.

The hydrochloride, $C_2H_5N.HCl$, crystallizes in six-sided prisms, united in tufts, and is extremely soluble in water, almost insoluble in absolute alcohol and ether.

The aurochloride, $C_2H_5N.HCl.AuCl_3$, forms shining,

golden-yellow, irregular plates, and when freshly precipitated it is easily soluble in water, alcohol, and ether, but the dried salt is incompletely soluble in water. The aqueous solution, treated with magnesium, gives off a sperm-like odor. Tho platinochloride crystallizes in prisms.

The phosphate, $(C_2H_5N)_2.H_3PO_4+3H_2O$ (?), forms prisms and slender double pyramids. It is difficultly soluble in hot water, insoluble in alcohol, easily soluble in dilute acids, alkalies, and alkali carbonates. It melts with decomposition at about 170°. It is probable that the above formula does not represent the salt as found, and from theoretical considerations LADENBURG is inclined to think that SCHREINER'S phosphate has the composition $(C_2H_5NH)_4Ca(PO_4)_2$.

LADENBURG and ABEL have recently (March, 1888) prepared a compound, ethyleneimine, which is isomeric, possibly identical with spermine. The reaction whereby it is prepared is similar to the one by which LADENBURG effected the synthesis of piperidine. Ethylenediamine hydrochloride is subjected to dry distillation, when it decomposes into ammonium chloride and the hydrochloride of the new base. Thus:

$$\begin{matrix} CH_2NH_2.HCl \\ | \\ CH_2NH_2.HCl \end{matrix} = \begin{matrix} CH_2 \\ | \\ CH_2 \end{matrix} \!\!>\!\! NH.HCl + NH_4Cl.$$

The nuclein of the spawn of salmon has been found by MIESCHER to exist in a salt-like combination with a basic substance, to which he applied the name protamine. PICARD has found it in the same source, together with hypoxanthine and guanine, but no xanthine. The formula assigned to this base is quite complex, and cannot be considered as definitely settled. Analysis of the platino-

chloride gave: Pt=24.64, Cl=26.45, N=15.03, C = 22.80, H=4.15, O=6.93. The hydrochloride forms an amorphous, hygroscopic, sticky mass.

Leucomaines of the Creatinine Group.

The knowledge of the formation of basic substances (ptomaines) in the presence of putrefaction of nitrogenous organic matter, led to a series of investigations having for their object the isolation of any alkaloidal bodies, if such existed, from the normal living tissues of the organism. A number of compounds possessing alkaloidal properties, such as the xanthine derivatives, already described, had been known for a long time, although their physiological relation to the animal economy was little, if at all, understood. Guareschi and Mosso, in the course of their researches on ptomaines, were among the first to direct their attention to the possible presence of ptomaine-like bodies in fresh tissues. They obtained in those cases where the extraction was carried on without the use of acids, only very minute traces of an alkaloidal body (possibly choline), and an inert substance, methyl-hydantoin, which, although it can scarcely be classed as a basic compound, is closely related to creatine, and for this reason will be described at the end of this section. Other Italian chemists, as Paternò and Spica and Marino-Zuco, had also shown that the normal fluids and tissues of the body were capable of yielding substances alkaloidal in nature, and these were regarded by them as identical with, or similar to, the ptomaines of Selmi.

Liebreich, in 1869, discovered in normal urine an oxidation-product of choline, probably identical with betaine (page 196), and Pouchet, in 1880, announced the presence in the same secretion of allantoin, carnine (page

280), and an alkaloidal base, which, however, was not obtained at that time in sufficient quantity to permit a determination of its character. Subsequently he succeeded in isolating this base as well as another closely related body, both of which will be described in their proper place. GAUTIER has been engaged for a number of years in the study of the leucomaines occurring in fresh muscle tissue, and he has succeeded in isolating several new compounds.

A number of these substances are credited with possessing an intensely poisonous action, and if such is the case it is very evident that any undue accumulation of such bases in the system, resulting from an interference in the elimination, may give rise to serious disturbances. The amount of these substances present in the daily yield of the urine is very small, so small, indeed, that we must rather look upon this small quantity as having escaped oxidation in the body. It is well known that the living tissues possess an enormous oxidizing and reducing power, and, according to GAUTIER, there is constantly going on in the normal tissues of the body a cycle of changes—the formation of leucomaines and their subsequent destruction by oxidation, before they have accumulated in sufficient quantity to produce poisonous effects.

The following method was employed by GAUTIER in his study of the leucomaines of muscle tissue: The finely divided fresh beef-meat or the Liebig's meat extract is treated with twice its weight of water, containing 0.25 gram of oxalic acid, and one to two c. c. of commercial peroxide of hydrogen per litre. The purpose of these precautions is to prevent fermentation. At the end of twenty-four hours the liquid is raised to the boiling-point, then filtered through linen, and the residue is thoroughly

squeezed. The filtrate is again raised to the boiling-point in order to coagulate any remaining albumen, and finally filtered through paper. The clear liquid thus obtained is evaporated in a vacuum at a temperature not exceeding 50°, and the acid syrupy residue is extracted with 99 per cent. alcohol; the alcoholic extract is in turn evaporated in a vacuum, and the residue taken up with warm alcohol of the same strength. The filtered alcoholic solution is set aside for twenty-four hours, and any deposit which forms is removed by filtration; ether (65°) is then added as long as a precipitate continues to form, and the whole is again allowed to stand for twenty-four hours. The ether-alcoholic filtrate from this precipitate is evaporated first on the water bath, and finally in a vacuum; the slight residue obtained contains a small quantity of basic substances possessing an odor of hawthorn.

The syrupy precipitate produced by the ether partially crystallizes on standing; a little absolute ether is then added, and after standing several days more the liquid is separated by means of an aspirator from the deposit of crystals (A). These are first washed with 99 per cent. alcohol, and then extracted with boiling 95 per cent. alcohol. The alcoholic solution, concentrated by evaporation, gives, on cooling, a deposit of lemon-yellow colored crystals of xantho-creatinine (B), from the mother-liquor of which there separates a crop of new crystals (C). The residue of the crystals (A) left after treatment with the boiling 95 per cent. alcohol is extracted with boiling water, which afterward gives a slight deposit of yellowish-white crystals of amphi-creatine (D). The aqueous mother-liquors on concentration yield another deposit of orange-colored crystals of cruso-creatinine (E). GAUTIER has, furthermore, separated three other bases from the mother-liquors

of the crystals obtained as above. Thus, a base which he named pseudoxanthine is stated to have been obtained by evaporating the alcoholic mother-liquors of B, D, E (?) in a vacuum, taking up the residue with water, and precipitating the hot solution with copper acetate. The precipitate is decomposed with hydrogen sulphide, and the aqueous solution, filtered whilst boiling hot, yields a deposit of a sulphur-yellow powder of pseudoxanthine. Thus, by the use of alcohol, ether, and water, GAUTIER, according to his statement, has succeeded in obtaining a sharp separation between these bases. The importance of the subject is such as to require not only confirmation of the results arrived at by GAUTIER, but also a more detailed and exact study of the chemical and physiological behavior of these bodies.

To the physiological chemist these substances are of especial interest because of the possible relation which they bear to the formation of creatine and creatinine in the muscle. It will be seen that in the leucomaines of this group, as well as in those of the uric acid group, hydrocyanic acid plays a very important part in the molecular structure of these bases. Just what the function of this cyanogen group is so far as the vital activity of the tissues is concerned we know very little, though recent investigations seem to show that the seat of the cyanogen formation lies within the nucleated cell, and is intimately connected with the functions of the nuclein molecule.

CRUSO-CREATININE, $C_5H_8N_4O$, forms orange-yellow crystals which are slightly alkaline in reaction, and possess a somewhat bitter taste. It yields a soluble, non-deliquescent hydrochloride crystallizing in bundles of needles; also a soluble platinochloride which forms tufts of beautiful, slender prisms. The aurochloride is obtained as slightly

soluble, crystalline grains, and, like the platinum double salt, is partially decomposed on heating. It is not precipitated by acetate of zinc or by mercuric nitrate, but is precipitated in the cold by solutions of alum. Zinc chloride produces in somewhat concentrated solutions a pulverulent precipitate which dissolves on heating, and recrystallizes again when it cools. Like xantho-creatinine it is not thrown out of solution by oxalic or nitric acid, and is thus distinguished from urea and guanidine ; nor is it precipitated by acetate of copper—a distinction from xanthine derivatives. Mercuric chloride produces an abundant flocculent precipitate which on heating partially dissolves, decomposing at the same time. Sodium phosphomolybdate gives a heavy yellow precipitate, whereas potassium mercuro-chloride and iodine in potassium iodide have no effect. Potassium ferricyanide is not reduced. This base differs in its composition from creatinine by HCN, the elements of hydrocyanic acid, but in its crystalline form and alkaline reaction, and some other properties, it would seem to be closely related to this latter substance. Because of this apparent relationship and its golden-yellow color, GAUTIER named it cruso-creatinine.

XANTHO-CREATININE, $C_5H_{10}N_4O$, is the most abundant of muscle leucomaines. It crystallizes in sulphur-yellow, thin spangles, consisting of nearly rectangular plates which resemble somewhat those of cholesterin. It is soft and talc-like to the touch ; possesses a slightly bitter taste, and when dissolved in boiling alcohol it gives off the odor of acetamide, though ordinarily in the cold it has a slight cadaveric odor. When heated, the substance evolves an odor of roast meat, carbonizes in part, and yields ammonia and methylamine. The crystals are amphoteric in reaction,

are soluble in cold water, and can be recrystallized from boiling 99 per cent. alcohol.

It forms a hydrochloride crystallizing in plumose needles, and a very soluble platinochloride; the aurochloride crystallizes with difficulty. Like creatinine, it is precipitated by zinc chloride; the yellowish-white precipitate dissolves with partial dissociation on warming, and on cooling separates as isolated or stellate groups of fine needles which possess the composition $(C_5H_{10}N_4O)_2ZnCl_2$. Silver nitrate throws down, in the cold, a flocculent precipitate which likewise dissolves on heating, and recrystallizes in needles. Mercuric chloride produces a yellowish-white precipitate. It is not precipitated by oxalic or nitric acid, nor by potassio-mercuric chloride, or iodine in potassium iodide. Tannin produces in time a slight turbidity, whilst sodium phosphomolybdate gives a heavy yellowish precipitate. This base is distinguished from the members of the uric acid group by not giving a precipitate with copper acetate, not even on heating.

On gentle oxidation with potassium permanganate it is converted into a black substance insoluble in acids and alkalies, and resembling azulmic acid. By treatment with recently precipitated mercuric oxide, it yields a substance which can be recrystallized from boiling 93 per cent. alcohol in needles which possess a slight alkaline reaction, and forms a slightly soluble, crystalline platinochloride. This new substance is precipitated from alcoholic solution by the addition of ether, as a mass of beautiful, white, silky needles resembling caffeine. These crystals melt at 174°; caffeine melts at 178°.

Xantho-creatine, given in fairly large doses, is poisonous, producing in animals depression, somnolence, and extreme fatigue, accompanied by frequent defecation and

vomiting. In its general properties this base resembles creatinine very much, and it was on account of this resemblance and its yellow color that it was named xantho-creatinine. This relation becomes especially evident since this base appears in the physiologically active muscle at the same time with creatinine, constituting sometimes one-tenth of the creatinine present. MONARI has found this base in the aqueous extract of the muscles of an exhausted dog, and also in the urine of soldiers tired by several hours' walk. He also demonstrated its presence in the urine of a dog after previous injection of creatinine.

AMPHI-CREATINE, $C_9H_{19}N_7O_4$, is slightly soluble and crystallizes from boiling water in yellowish-white oblique prisms, which possess, if any, a slightly bitter taste. When heated to 100° it decrepitates somewhat, and at 110° it becomes opaque white. Potassium hydrate does not decompose it in the cold. Although a weak base, it combines to form salts just as the preceding members of this group. The hydrochloride is crystalline, and is not deliquescent; the platinochloride forms rhombic plates, which are soluble in water, but are insoluble in absolute alcohol; the aurochloride crystallizes in easily soluble, very small, microscopic crystals, which are tetrahedral to hexahedral in their habit. It is not precipitated by copper acetate or by mercuric chloride; nor does it give the murexide test, or the xanthine reaction. Sodium phosphomolybdate produces a yellow, pulverulent precipitate. In its properties it resembles creatine, and indeed GAUTIER thinks it may be possibly a combination of creatine, $C_4H_9N_3O_2$, and a base $C_5H_{10}N_4O_2$, which, it will be seen, differs from the former only by a HCN group. This second compound, if it really exists, has an analogy in

cruso-creatinine, the relation of which to creatinine may be expressed by the equation :

$$\underset{\text{Cruso-creatinine.}}{C_5H_8N_4O} = \underset{\text{Creatinine.}}{C_4H_7N_3O} + HCN.$$

In a similar manner, amphi-creatine may be regarded as

$$\underset{\text{Amphi-creatinine.}}{C_9H_{19}N_7O_4} = 2\underset{\text{Creatinine.}}{C_4H_9N_3O_2} + HCN.$$

A Base, $C_{11}H_{24}N_{10}O_5$, was isolated by Gautier from the mother-liquors of xantho-creatinine. It crystallizes in colorless or yellowish, thin, apparently rectangular plates, which are tasteless, and possess an amphoteric reaction. The hydrochloride forms bundles of fine needles ; the sulphate yields a confused mass of needles ; the platinochloride is soluble, non-deliquescent, and crystalline. When heated with water in a sealed tube at 180°–200°, it gives off ammonia and carbonic acid, and is converted into a new base, which, however, has not been studied. This reaction may be expressed by the equation :

$$C_{11}H_{24}N_{10}O_5 = 2C_5H_{10}N_4O_2 + \underset{\text{Urea.}}{CO(NH_2)_2}$$

The urea which at first forms, is, in turn, decomposed, thus :

$$CO(NH_2)_2 + H_2O = CO_2 + 2NH_3.$$

It is to be observed that this base differs in composition from the following one by HCN, the hydrocyanic acid molecule.

A Base, $C_{12}H_{25}N_{11}O_5$, was obtained from the mother-liquors of cruso-creatinine, and forms rectangular silky plates, resembling those of the preceding base and of xantho-creatinine. It forms crystallizable salts.

These complex bases will require further study in order

to elucidate their physiology, and the possible connection which they may have with the formation of urea, and of the creatinine derivatives already described.

METHYL-HYDANTOIN, $C_4H_6N_2O_2 = CO\begin{matrix}N(CH_3).CH_2\\NH - CO\end{matrix}$. —This substance was obtained by GUARESCHI and MOSSO (1883), by extracting fresh meat with 1–1.5 volumes of water (without addition of acid), for two hours at 50°–60°. The aqueous extract was evaporated on the water bath and the residue was extracted with 95 per cent. alcohol. This alcoholic solution, after the alcohol was driven off, was taken up in water, filtered, and the aqueous solution was first extracted with ether, then rendered alkaline with ammonia, and again extracted with ether. The alkaline ether extract gave on evaporation a white crystalline residue of methyl-hydantoin. The amount of this substance present in flesh appears to be quite variable, since, at times, none whatever can be extracted. ALBERTONI has isolated it from dog's flesh. Previous to its discovery in flesh by GUARESCHI and MOSSO, it was known for a long time as a decomposition-product of various nitrogenous bases of the body. Thus, NEUBAUER prepared it by heating creatinine with barium hydrate, whilst HUPPERT obtained it by fusing together sarcosine with urea. As it occurs in muscle it is probably derived from the creatine, though under what conditions this splitting up takes place is not definitely known. Acetic and lactic acids are incapable of effecting this change. At all events, it belongs to the ureides, and is intermediate between creatinine, sarcosine, and urea.

Methyl-hydantoin forms prisms which are easily soluble in water and alcohol, and but slightly soluble in cold ether.

It melts at 156° (Salkowski); at 159°–160° (Guareschi and Mosso). Its aqueous solution is slightly acid in reaction. On strong heating it volatilizes. When fused with potassium hydrate it gives off ammonia; it reduces mercuric nitrate in the cold. Treated with mercuric oxide it assumes an alkaline reaction, and the filtrate on heating yields metallic mercury. With silver oxide it forms pearly lanceolate plates having the composition $C_4H_5N_2O_2.Ag$. It does not give any alkaloidal reactions.

Undetermined Leucomaines.

Leucomaines of Expired Air.

It was shown at quite an early period that exhalations from animals contain, besides an increased amount of carbonic acid, some organic matter, the nature of which, on account of the exceedingly minute quantity in which it occurs, has never been satisfactorily determined. Nevertheless, various observers did not hesitate to ascribe to it the ill effects consequent upon breathing impure air, whilst at the same time the carbonic acid formed during respiration was considered either as entirely inert, or as insignificant in its action. Thus, respired air from which moisture and carbonic acid have been removed, but which still contains the organic vapors, has been found to be highly poisonous. On the other hand, if the respired air is drawn through a red-hot tube to destroy the organic matter, the air thus purified is capable of sustaining life even in presence of a large percentage of carbonic acid. Whilst it cannot be, therefore, doubted that the organic matter of expired air plays a most important part in producing the well-known noxious effects resulting from breathing confined and vitiated air, nevertheless it would seem from experiments made by

Angus Smith that the increase of even such small quantities of carbonic acid in the air, as from 0.04, the normal amount present, to 0.1 per cent., is capable of producing systemic disturbances characterized by a decrease in the pulse-rate and an increase in the rate of respiration.

Smith is consequently of the opinion that the constant lowering of the pulse in impure air occasioned by the presence of carbonic acid, must have a depressing effect on the vitality. Whatever ill effects the carbonic acid may produce of itself, it remains certain that this gas is not the most potent and most injurious constituent of respired air; and the investigations of Hammond, Nowak, Seegen, and others, point conclusively to the organic matter as the direct and immediate agent which produces those symptoms of sickness and nausea experienced in badly ventilated closed rooms.

Of special importance to the sanitarian and physician is the recent work on the nature and action of the poisonous principle of expired air, which has been made by Brown-Séquard, d'Arsonval, and R. Wurtz. The first two observers found that the vapors exhaled by dogs, when condensed, and the aqueous liquid (20–44 c. c.) thus obtained was injected into other animals death was produced, mostly within twenty-four hours. The symptoms observed were dilatation of the pupil, increase of heart-beat to 240–280 per minute, which may last for several days or even weeks, whilst the temperature remains normal; the respiratory movements are generally slowed, and usually there is observed considerable paralysis of the posterior members. Choleraic diarrhœa is invariably present. As a rule, it appears that larger doses cause labored respiration, violent retching, and contraction of the pupil. A rapid lowering of temperature, 0.5° to 5°, is sometimes

observed. These same symptoms, apparently in aggravated form, were obtained when the liquid had been previously boiled for the purpose of destroying any germs that might be present. The appearances presented on post-mortem were much like those observable in cardiac syncope. From their results it is evident that expired air contains an extremely violent poison, and BROWN-SÉQUARD is of the opinion that in confined air the continuous, though slowly exercised influence of this volatile poison produces pulmonary phthisis.

The above work has already been confirmed, in part, by R. WURTZ, who, by passing expired air through a solution of oxalic acid, has obtained besides ammonia a volatile organic base which is precipitated by BOUCHARDAT'S reagent and by potassio-mercuric iodide. It is said to form a platinum double salt crystallizing in short needles, and a soluble gold salt. When heated to 100° it gives off a peculiar odor. This basic substance may properly be looked upon as a leucomaine.

Sewer-air, according to observations made by ODLING, contains a basic substance which is probably in composition a compound ammonia. It contains, however, more carbon than methylamine and less than ethylamine.

It should be remarked that JACKSON has recently (Dec. 1887) announced the presence in expired air of quantities of carbon monoxide gas sufficient to produce the ill effects ordinarily attributed to the organic matter. The presence of this poisonous gas must first be fully demonstrated before it can be taken into account in the consideration of the toxicity of air; certainly, even if present, it cannot explain the results obtained by the French investigators as stated above.

Leucomaines of the Urine

A number of basic substances have been isolated at different times from the urine, and on that account they may be properly classed as leucomaines. Thus, LIEBREICH (1869) found in the urine a base which apparently was an oxidation-product of choline, and which has since been regarded as identical with betaine. Most of the members of the uric acid group of leucomaines have been detected in the urine and on account of their well-defined nature they are described by themselves.

In 1879, THUDICHUM announced the presence in the urine of four new alkaloids, one of which was subsequently rediscovered by SALOMON and named paraxanthine (page 258). Another base which was obtained and termed reducine, yielded a barium salt which readily reduced the salts of silver and mercury. Its formula probably corresponds to $C_{12}H_{24}N_6O_9$ or $C_6H_{11}N_3O_4$. A third alkaloid formed a zinc compound having the composition $C_6H_9N_3O.ZnO$. A fourth base is said to give a compound with platinum chloride, and to contain an aromatic nucleus.

In 1880, POUCHET announced the presence of carnine, $C_7H_8N_4O_3$, and of another base which he subsequently analyzed and found to have either the composition $C_7H_{12}N_4O_2$ or $C_7H_{14}N_4O_2$. This substance formed deliquescent fusiform crystals, sometimes crystallized in bundles or irregular spheres, which possessed a slightly alkaline reaction and combined with acids to form crystallizable salts. It was soluble in dilute alcohol, almost insoluble in strong alcohol, insoluble in ether. The hydrochloride yielded double salts with gold chloride, platinum chloride, and mercuric chloride. The platinochloride formed deliquescent golden-yellow rhombic prisms. This base occurred in the dialysate (see

page 211). From the non-dialyzable portion, POUCHET obtained another base corresponding to the formula $C_3H_5NO_2$. It yields precipitates with the general alkaloidal reagents, is altered on exposure to air, and is resinified by hydrochloric acid. On the addition of platinum chloride it is rapidly oxidized, but does not yield a platinochloride. The same author regards the urine as containing very small quantities of some pyridine bases which are analogous or identical with those obtained by GAUTIER and ETARD from decomposing fish.

The distinguished Italian toxicologist SELMI was perhaps the first to draw attention to the probable formation of basic substances in the living body during those pathological changes brought on by the presence of pathogenic germs; and in a memoir presented to the Academy of Sciences of Bologna, in December, 1880, he announced that infectious diseases, or those in which there occurs an internal disarrangement of some element, either plasmic or histological, must be accompanied or followed by an elimination of more or less characteristic products, which would be a sign of the pathological condition of the patient. To support this theory, he examined a number of pathological urines and succeeded in obtaining from them basic substances some of which were poisonous, others not. Thus, a specimen of urine from a patient with progressive paralysis gave two bases strongly resembling nicotine and coniine; from other pathological urines the bases obtained usually had either an ammoniacal or trimethylamine odor. An apparent strong confirmation of SELMI'S theory is seen in the observations made by BOUCHARD, VILLIERS, LEPINE, GAUTIER, and others, all of whom have found basic substances in the urine of various diseases. Unfortunately none of these bases supposedly characteristic of patho-

logical urines have been isolated in a chemically pure condition; nor has the study of normal urine been carried sufficiently far to show the positive absence of such bodies.

Leucomaines of the Saliva.

According to the statement of GAUTIER (1881), normal human saliva contains divers toxic substances in small quantities which differ very much in their action according to the time of their secretion, and probably according to the individual gland in which they are secreted. The aqueous extract of saliva at 100° is poisonous or narcotic in its action toward birds. To show the presence of basic substances, the aqueous extract was slightly acidulated with dilute hydrochloric acid, then precipitated by MAYER'S reagent; the precipitate was washed, then decomposed by hydrogen sulphide, and the solution filtered. The filtrate on evaporation gave a residue consisting of microscopic slender needles of a soluble hydrochloride. This salt, purified by extraction with absolute alcohol, forms soluble crystalline, but easily decomposable double salts with platinum chloride and with gold chloride. The solution of the hydrochloride produces an immediate precipitate of Prussian blue in a mixture of potassium ferricyanide and ferric chloride, and when injected into birds produces a condition of stupor.

Leucomaines from other Tissues of the Body.

SELMI'S work upon the formation of ptomaines during the process of putrefaction led many investigators to doubt the exact origin of these bases as due to the decomposition of the proteid or other complex molecules. To substantiate this, a number of chemists, especially Italian, endeav-

ored to show that SELMI'S bases, to a large extent at least, exist preformed in the various tissues. PATERNÒ and SPICA (1882), succeeded in extracting from fresh blood as well as from fresh albumen of eggs substances identical, or at least similar, to those designated under the name of ptomaines. Their observations, however, were confined to the detection of alkaloidal reactions in the various extracts obtained by DRAGENDORFF'S method, and at no time were they in possession of a definite chemical individual. MARINO-ZUCO (1885) was more successful, inasmuch as he succeeded in obtaining from fresh tissues and organs relevant quantities of a base identical with choline, and, in addition, he obtained extremely minute traces of other alkaloidal bodies. One of these, obtained by the STAS method from the liver and spleen of an ox, exhibited in hydrochloric acid solution a beautiful violet fluorescence resembling very much that of the salts of quinine. A similar base, probably identical with this one, was obtained by BENCE JONES and DUPRÉ (1866) from liver, nerves, tissues, and other organs, and was named by them "animal chinoidine." A greenish-blue fluorescence is frequently observable in the alcoholic extracts of decomposing glue as well as from other putrefying substances. From a number of very thorough experiments, he concluded that basic substances do not preëxist in fresh organs, but that the acids employed in the process of extraction exert a decomposing action upon the lecithin present in the tissues, resulting in the formation of choline. He further showed that the method of DRAGENDORFF, on account of the larger quantity of extractives which form, invariably gave a larger yield of this base than did the STAS-OTTO method. Similar observations were made by GUARESCHI and MOSSO, by COPPOLA and others. At the present time there is no

doubt that some basic substances, among these choline, can be formed by the action of reagents, and, on the other hand, it is equally well demonstrated that similar bases do preëxist in the physiological condition of the tissues and fluids of the body.

Recently R. Wurtz has obtained from normal blood a number of crystalline products of alkaline reaction, which form well-crystallizable double salts with gold, platinum, and mercuric chlorides. These, however, have not been as yet subjected to analysis, because of the minute quantities which were isolated.

A substance of uncertain character has been isolated by Capitan and Charrin from blue pus, and named pyocyanine. Dilute sulphuric acid withdraws it from the chloroformic solution and at the same time becomes red. It is said to reduce ferric salts, but beyond this nothing definite is known as to the nature or origin of this substance.

Morelle (1886) showed the presence in the spleen of the ox of a base, the hydrochloride of which crystallized in deliquescent needles and likewise formed crystalline platino- and aurochlorides. From experiments made by Laborde, the base would seem to possess decided toxic properties, bringing on a dyspnœic condition with convulsive movements and loss of motion. The post-mortem examinations revealed an extended visceral œdematous infiltration, and stoppage of the heart in systole.

A. W. Blyth has claimed to have isolated from milk two alkaloidal substances, namely galactine, the lead salt of which is said to have the formula $Pb_2O_3C_{54}H_{18}N_4O_{25}$, and lactochrome, the mercury salt of which is represented by the formula $HgOC_6H_{18}NO_6$.

Leucomaines of the Venoms of Poisonous Serpents

The study of the chemistry of the venoms of serpents and of batrachians is fraught with so many difficulties and with so much danger, that we cannot wonder at the present unsatisfactory condition of our knowledge in regard to the poisonous principles which they contain. Much of the work that has been done hitherto is not only inaccurate and very contradictory, but is far from meeting the requirements of exact toxicological research. From recent investigations it seems, however, to be quite certain that the most active constituent of the venoms of serpents is not alkaloidal in its nature as has been supposed by some. In 1881 GAUTIER announced the isolation of two alkaloids from the venom of the cobra which gave precipitates with tannin, MAYER'S reagent, NESSLER'S reagent, iodine in potassium iodide, etc. They formed crystallizable platinochlorides and aurochlorides, and also crystalline, neutral, somewhat deliquescent hydrochlorides. The neutral or slightly acid solutions produced an immediate precipitate of Prussian blue in a mixture of potassium ferricyanide and ferric chloride. These substances possess a decided physiological action, though GAUTIER himself does not consider them to be the most dangerous constituents of the venoms. This observation of GAUTIER as to the presence of distinct basic substances in venoms is at variance with that of WOLCOTT GIBBS, who has been unable to obtain an alkaloid from the rattlesnake (Crotalus) venom. S. WEIR MITCHELL and E. T. REICHERT likewise state that they have been utterly unable to substantiate GAUTIER'S statements. Still more recently WOLFENDEN, in an elaborate paper on the nature of cobra venom, has confirmed WOLCOTT GIBBS as to the entire absence of any alkaloidal body.

MITCHELL and REICHERT have made a careful study of the venoms of various serpents, such as cobra, rattlesnake, moccasin, and Indian viper, and have succeeded in isolating two proteid constituents, one belonging to the class of globulins and the other to the peptones. According to them, the globulin constituent consists of at least three distinct globulins. They found that boiling coagulates and destroys the globulin as a poison, but leaves the venom peptone toxically unchanged, so that the venom, though still poisonous, fails to produce the characteristic local lesions due to fresh or unboiled venom. On the other hand, GAUTIER asserts that the venom is not sensibly altered on being heated to 120°–125°, and that the toxic action remains constant even when all the proteid constituents are removed, thus showing that the toxic action cannot be attributed to the albuminoids. The venom peptone from the rattlesnake or the moccasin, however, when injected into animals produced toxic effects which were marked by an œdematous swelling over the site of injection; the tumor was filled with serum, and so also was the subcutaneous cellular tissue. Furthermore, a gradual breaking down of the tissues occurred, accompanied by rapid putrefactive changes and a more or less extensive slough. That peptones may possess intensely poisonous properties has been shown to be the case by a number of authors, among whom may be mentioned SCHMIDT-MÜLHEIM, HOFMEISTER, POLLITZER, and others. BRIEGER has, moreover, demonstrated that the formation of peptones in the process of digestion is accompanied by the development of a toxic ptomaine which he has named peptotoxine.

The venom globulins, on the other hand, though present in less quantity than the peptones, induced the same re-

markable local effects seen on injection of the pure venom. They cause local bleedings, destroy the coagulability of the blood, and rapidly corrode the capillaries.

These results of MITCHELL and REICHERT, which are given here somewhat in full, have been questioned by WOLFENDEN, who, whilst agreeing in the main that the poisonous property of venom is due to proteid constituents, regards their peptone not as a true peptone, but rather as one or more bodies of the albumose group of proteids. He likewise regards the globulin of moccasin venom to be some other proteid body. According to him, the cobra venom owes its toxicity to the proteids, globulin, serum-albumin, acid albumin. Occasionally there seem to be present traces of peptone and of hemialbumose.

In view of this evidence of the poisonous nature of some proteids, and of the absence of true alkaloidal bodies, BRIEGER thinks it inadmissible to consider globulins and peptones as the toxic principles of venoms. He is apparently inclined to believe that their action is due to animal alkaloids on the ground that these bases are extremely soluble, and hence always go into solution along with the likewise very soluble proteid constituents, and that the difficulty in their isolation lies in the elimination of these proteids.

CLOËZ and GRATIOLET in 1852 examined the poison contained in the cutaneous pustules of some batrachians, and succeeded in extracting a substance which gave a white precipitate with mercuric chloride and formed a platinum double salt. Beyond this meagre information very little is known in regard to the character of these poisons, though ZALESKY, in 1866, announced the isolation of an alkaloid to which he assigned the formula $C_{34}H_{60}N_2O_5$, and which

he named samandarine. According to CALMEIL, the poison from the toad contains methyl-carbylamine and isocyanacetic acid.

TABLE OF LEUCOMAINES.

Formula.	Name.	Discoverer.	Source.	Physiological action.
$C_5 H_5 N_5$	Adenine.	Kossel.	Nuclein-containing organs.	Non-poisonous; muscle stimulant.
$C_5 H_4 N_4 O$	Hypoxanthine.	Scherer.	Nuclein-containing organs.	Non-poisonous; muscle stimulant.
$C_5 H_5 N_5 O$	Guanine.	Unger.	Nuclein-containing organs, guano.	Non-poisonous; muscle stimulant.
$C_5 H_4 N_4 O_2$	Xanthine.	Marcet.	Nuclein-containing organs, calculi.	Non-poisonous; muscle stimulant.
$C_6 H_6 N_4 O_2$	Heteroxanthine.	Salomon.	Urine.	
$C_7 H_8 N_4 O_2$	Paraxanthine.	Thudichum. Salomon.	"	
$C_7 H_8 N_4 O_3$	Carnine.	Weidel.	Liebig's meat extract.	Non-poisonous; muscle stimulant.
$C_4 H_5 N_5 O$	Pseudoxanthine(?)	Gautier.	Muscle.	
$C_2 H_5 N$	Spermine.	Schreiner.	Sperma, in tissues of leucocythæmics.	
$C_5 H_8 N_4 O$	Cruso-creatinine.	Gautier.	Muscle.	
$C_5 H_{10} N_4 O$	Xantho-creatinine.	"	"	Poisonous.
$C_9 H_{19} N_7 O_4$	Amphi-creatine.	"	"	
$C_{11} H_{24} N_{10} O_5$	Unnamed.	"	"	
$C_{12} H_{25} N_{11} O_5$	"	"	"	
$C_7 H_{12} N_4 O_2$	"	Pouchet.	Urine.	
$C_3 H_5 NO_2$	"	"	"	

CHAPTER VIII.

THE PATHOLOGICAL IMPORTANCE OF THE LEUCOMAINES.

WHILE the medical profession has been giving much time, attention, and energy in recent years to the study of infectious diseases, it has too much neglected a large and important class of ailments which arise within the body itself, and which may be called autogenous. It is true, without exception, so far as we know, that the excretions of all living things, plants and animals, are poisonous to the organisms which excrete them. A man may drink only chemically pure water, eat only that food which is free from all adulteration, and breathe nothing but the purest air, free from all organic matter, both living and dead, and yet that man's excretions would contain poisons. Whence do these poisons originate? They are formed within the body. They originate in the metabolic changes by which the complex organic molecule is split up into simpler compounds. We may suppose—indeed, we have good reasons for believing—that the proteid molecule has certain lines of cleavage along which it breaks when certain forces are applied, and that the resulting fragments have also lines of cleavage along which they break under certain influences, and so on until the end-products, urea, ammonia, water, and carbonic acid gas, are reached: also that some of these intermediate fragments are highly poisonous compounds has been abundantly demonstrated. The fact that the hydrocyanic acid molecule is a frequent constituent of the leucomaines, as has been shown in the preceding pages, is one of great significance.

We know that chemical composition is an indication of physiological action, and the intensely poisonous character of some of the leucomaines conforms to this fact. It matters not whether the proteid molecule be broken up by organized ferments, germs, or by the unorganized ferments of the digestive juices, or by those still unknown agencies which induce metabolic changes in all the tissues—in all cases poisons are formed. These poisons will differ in quality and quantity according to the proteid which is acted upon, and according to the force which acts, but still they will be poisonous.

While it is true that germs are constantly present in the human intestines, and that they undoubtedly act upon our food, there is no more reason for believing that they are concerned in the actual production of all the leucomaines, than there is for believing that bacteria produce morphine in the poppy. The old theory, that the chemistry of the plant is altogether synthetical, and the chemistry of the animal altogether analytical, has long since been exploded. The formation of carbonic acid from more complex molecules in the plant, and the conversion of ammonia into urea in the animal, are illustrations from a large class of well-established facts which have proved fatal to the old theory.

But we shall not dwell upon the origin of the animal alkaloids, as the time has not yet come for positive statements on the subject. We know that they are formed in the body, that they are contained in the excretions, and that any disturbance between the rate of their formation and their excretion is followed by a corresponding disturbance of the health.

In the first place, although peptones cannot be classed with alkaloidal bodies, they represent the first known step

in the breaking up of the proteid molecule, and a word concerning their physiological effects may not be out of place. When injected directly into the circulation, peptones act as powerful poisons. They destroy coagulability of the blood, lower blood-pressure, and, in large quantities, cause speedy death. In health the peptones formed during digestion do not reach the general circulation. In the liver they are robbed of their poisonous properties by being converted into globulin. But it is altogether probable that at times the liver partially fails in this function, and that the health suffers in consequence. This may be due to the taking of excessive quantities of proteids, the digestion being active and the peptones formed and poured into the portal circulation faster than the liver can convert them into globulin; or it may be that from lack of exercise or other reason the liver is tardy in its action, or "torpid" as we say, and small quantities of peptones pass into the general circulation. The lassitude, depression, sense of weight in the limbs, and dulness in the head occurring in the well-fed, inactive man after his meals, BRUNTON attributes to poisoning with peptones. The remedy is less food, especially less nitrogenous food, and more exercise. That some substance resulting from the proteids of the food is the cause of this trouble, BRUNTON thinks is evidenced by the fact that "the weakness and languor are apparently less after meals consisting of farinaceous food only."

BRIEGER obtained by digesting fibrin with gastric juice a substance which gives reactions with many of the general alkaloidal reagents, and to which he has given the name peptotoxine. A few drops of a dilute aqueous solution of this substance sufficed to kill frogs within fifteen minutes. The frogs became apparently paralyzed and did not respond to stimuli. Slight tremor was perceptible in the muscles

of the extremities. Rabbits of about one kilogram weight were given from 0.5 to 1 gram of the extract subcutaneously. About fifteen minutes after the injection, gradual paralysis set in in the posterior extremities; the animal fell into a soporific condition, sank and died. In some rabbits several hours elapsed before the above-mentioned symptoms appeared.

Peptotoxine was also found by BRIEGER as one of the first putrefactive products of proteids, as fibrin, casein, brain substance, liver, and muscle. But after putrefaction had continued for eight days or longer, peptotoxine disappeared.

It is highly probable that many of the nervous symptoms which accompany dyspepsia are due to the formation and absorption of poisonous substances.

In some persons the tendency to the formation of poisons out of certain foods is very marked. Thus, there are some to whom the smallest bit of egg is highly poisonous; with others, milk will not agree; and instances of this kind are sufficiently numerous to give rise to the adage, "What is one man's meat is another man's poison."

BRUNTON is of the opinion that the condition which we term "biliousness," and which is most likely to exist in those who eat largely of proteids, is due to the formation of poisonous alkaloids.

We will venture the assertion that ordinary colds are best explained by the supposition that certain effete matters, which are normally excreted by the skin, are retained. This is borne out by the effects on the nervous system, and by the fact that the only successful methods of treatment are essentially eliminative.

That certain febrile conditions are autogenous there can scarcely be a doubt. These, like other diseases originating

within the system, may be due to either of the following causes: (1) There may be an excessive formation of poisons in the body. Thus, BOUCHARD has shown that the urine excreted during the hours of activity is much more toxic than that excreted during the hours of rest. Both physical and mental labor are accompanied by the formation of these poisonous substances, and if the hours of labor are prolonged and those of rest shortened, there will be an accumulation of effete matters within the system. (2) The accumulation of the poisonous matters may be due to deficient elimination.

First, we may mention fatigue fever, which is by no means uncommon, and from which the busy physician not infrequently suffers. One works night and day for some time; elimination seems to proceed normally; but after a few days there is an elevation of temperature of from one to three degrees, the appetite is impaired, and then if the opportunity for rest is at hand sleep is impossible. The tired man retires to his bed expecting to fall asleep immediately, but he tosses from side to side all night, or his sleep is fitful and unrefreshing. The brain is excited and refuses to be at rest.

Fatigue fever is frequently observed in armies upon forced marches, especially if the troops are young and raw. MOSSO has recently studied this fever in the Italian army. He states that in fatigue the blood is subjected to a process of decomposition brought about by the infiltration into it from the solid tissues of poisonous substances, which when injected into the circulation of healthy animals induce malaise and all the signs of excessive exhaustion.

This fever is sometimes pronounced malarial, and quinine is administered, but it does no good, often harm by increas-

ing cerebral excitement. The proper treatment is prolonged rest.

Then there is the fever of exhaustion, which differs from fatigue fever only in degree. It is brought on by prolonged exertion without sufficient rest and often without sufficient food. The healthy balance between the formation and excretion of poisons is disturbed, and it may be weeks before it is reëstablished—indeed, it may never be reëstablished, for some of these cases terminate fatally. The fever of exhaustion may take on the typhus form, delirium may appear, muscular control of the bowels may be lost, and death may result.

Between these extremes of fatigue fever and the fever of exhaustion there may be every degree of fever from over-exertion. Then again, there is the fever of non-elimination, which all physicians of experience have observed. There is a feeling of languor, the head aches, the tongue is coated, the breath offensive, and the bowels constipated. The physician fears typhoid fever, but finds that a good, brisk cathartic dissipates all the unpleasant symptoms, and the temperature falls to the normal. This fever is also liable to appear among those who are confined to bed from other causes. BRUNTON says: "No one who has watched cases of acute disease, such as pneumonia, can have failed to see how a rise of temperature sometimes coincides with the occurrence of constipation, and is removed by opening the bowels." The surgeon and obstetrician have often had cause to rejoice when they have found a fever which they feared indicated septicæmia disappearing after free purgation.

BOUCHARD has shown that normal fæces contain a highly poisonous substance which may be separated from them by dialysis, and which, when administered to rabbits,

I.—Tabular View of the Reactions of Certain Ptomaines.

	Trimethylamine Hydrochloride, $N(CH_3)_3.HCl$	Diethylamine Hydrochloride, $N(C_2H_5)_2H.HCl$	A Base (p. 150), [illegible]	Ethylidenediamine Hydrochloride, $C_2H_8N_2.2HCl$	P[illegible]	Cadaverine, $C_5H_{14}N_2$	Putrescine Hydrochloride, $C_4H_{12}N_2.2HCl$	Cadaverine Hydrochloride, $C_5H_{14}N_2.2HCl$	Neuridine Hydrochloride, $C_5H_{14}N_2.2HCl$	Methyl-guanidine Hydrochloride, $C_2H_7N_3.HCl$	Neurine Chloride, $C_5H_{12}N.Cl$	Choline Chloride, $C_5H_{14}NO.Cl$	Betaine Chloride, $C_5H_{12}NO_2.Cl$	Typhotoxine Hydrochloride, $C_7H_{17}NO_2.HCl$	A Base (p. [illegible]), $C_7H_{17}NO_2.HCl$	Base from Cultures of Typhoid Bacillus (Baginsky, [illegible])	Mydaleine Hydrochloride.	Peptotoxine.	Hoffa's Ptomaine of Anthrax Bacillus.	Ptomaine from Cultures of Staphylococcus pyogenes aureus.
Phosphotungstic acid.	White crystalline precipitate, easily soluble in water.	———	Yellowish-white precipitate.	———	White precipitate, soluble in excess.	White precipitate, easily soluble in excess.	White precipitate.	White precipitate, easily soluble in excess.	White amorphous precipitate, soluble in excess.	———	*	White precipitate, insoluble in water, on standing becomes crystallized.	White precipitate, soluble in excess.	White crystalline precipitate.	White precipitate.	———	White precipitate, soluble in excess.	Voluminous white precipitate.	White precipitate.	White precipitate, soluble in excess.
Phosphomolybdic acid.	White granular precipitate.	Yellow precipitate.	Heavy yellow precipitate, difficultly soluble in NH_4OH, no blue color.	White precipitate.	Yellow precipitate.	White crystalline precipitate, soluble in excess.	Yellow precipitate.	White crystalline precipitate; yellow precipitate (Bocklisch).	White crystallized precipitate.	Yellow crystalline precipitate.	White crystalline precipitate, insoluble in excess.	Voluminous precipitate.	Yellow precipitate.	Yellow crystalline precipitate.	Yellow precipitate.	White precipitate.	Yellow amorphous precipitate.	Id.	Heavy yellow precipitate.	Yellow flocculent precipitate.
Phosphoantimonic acid.	———	Precipitate easily soluble in excess.	———	Yellowish-white precipitate, soluble in excess.	———	White crystalline precipitate.	———	White precipitate, soluble in excess.	White flocculent precipitate.	———	White, voluminous precipitate.	White curdy precipitate.	A precipitate, readily soluble in excess.	———	———	———	———	———	Voluminous white precipitate.	———
Picric acid.	Yellow precipitate, crystallizing in needles.	———	First amorphous, then assumes cauliflower shape.	———	Yellow needles.	Yellow needles.	Well-formed, difficultly soluble broad needles.	Yellow needles.	Precipitates slowly in beautiful yellow needles.	———	———	———	Yellow needles.	Difficultly soluble precipitate.	*	———	Yellow oily precipitate.	———	Clear yellow precipitate.	Yellow needles.
Tannic acid.	———	———	Whitish precipitate.	———	Dirty white precipitate.	White amorphous precipitate.	———	———	*	———	Dirty white voluminous precipitate.	*	———	———	———	Yellowish-white amorphous precipitate.	———	———	White granular precipitate.	———
Potassium bismuth iodide.	Red precipitate.	Brick-red precipitate.	———	Precipitate of red plates.	Oily precipitate, soon becomes crystalline.	Brown precipitate.	First amorphous, then crystallizes in needles.	Red needles.	Red amorphous precipitate.	Brick-red precipitate.	Red amorphous precipitate.	Red amorphous precipitate.	Brick-red precipitate.	Resinous precipitate.	Brick-red amorphous precipitate.	Reddish-brown precipitate.	Dirty brown oily precipitate.	———	———	Reddish-brown needles.
Potassium mercuric iodide.	Yellowish precipitate.	Oily precipitate, soon becomes granular.	Whitish precipitate.	———	Id.	Resinous precipitate.	Id.	———	*	———	Yellowish-white, voluminous precipitate.	Yellowish crystalline precipitate.	Clear yellow, oily precipitate, soluble in excess.	Oily drops which do not become crystalline.	At first an oily precipitate, which soon solidifies to needles.	Yellowish-white precipitate.	Yellow oily precipitate.	A compact yellow precipitate.	Golden-yellow precipitate.	———
Potassium cadmium iodide.	Yellowish-white crystalline precipitate.	———	———	———	Id.	———	———	———	*	———	White precipitate.	———	———	Id.	Id.	———	———	Id. Cadmium [illegible] iodide — a red precipitate.	———	Faint rose color.
Gold chloride.	———	———	Yellow crystalline precipitate.	———	———	———	———	———	Crystalline precipitate.	———	A precipitate.	———	———	———	———	———	Oily drops.	A precipitate.	———	———
Platinum chloride.	———	———	Heavy yellow precipitate.	———	———	———	———	———	———	———	A precipitate.	———	———	———	———	———	Microscopic needles united in tufts.	*	Yellowish precipitate.	———
Mercuric chloride.	———	Precipitate in concentrated solution. Ammonium $HgCl_3$ — 0.	White precipitate.	———	———	———	———	———	*	* Ammonium $HgCl_3$ gives precipitate in conc. solution.	White granular precipitate.	White granular precipitate.	A precipitate of short prisms, rather easily soluble.	———	———	———	———	A precipitate.	Yellowish-white precipitate.	———
Iodine in potassium iodide.	Brown precipitate, solidifying after some time in plates.	Brown oily precipitate.	Kermes colored precipitate.	———	———	Brown precipitate.	Brown crystalline precipitate.	Brown needles.	*	Oily drops.	Brown amorphous precipitate.	Brown granular precipitate.	Oily precipitate.	Id.	Id.	Brown precipitate.	Dirty brown oily precipitate.	Brown precipitate.	Brownish-yellow precipitate.	———
Iodine in hydriodic acid.	Id.	Id.	Id.	———	———	Id.	Id.	Id.	*	Id.	Id.	A precipitate of fine needles.	Crystalline precipitate.	Id.	Id.	———	Id.	Id.	———	Oily drops.
Ferric chloride and potassium ferricyanide.	———	———	Immediate Berlin blue precipitate.	———	———	When perfectly pure, no blue color.	———	No blue color when pure.	?	———	———	———	After a time gives a blue coloration.	———	*	———	Immediate intense blue color.	Berlin blue.	———	Intense blue color.
Potassium bichromate and conc. sulphuric acid.	———	———	Potassium [illegible] — yellow, hardly crystalline precipitate.	———	———	———	———	Reddish-brown precipitate which soon disappears.	Fröhde's reagent — 0.	———	———	———	Ammonium $ZnCl_3$ — needles.	———	———	———	———	———	———	———

To face page [illegible].

Table II.—

Note.—The greater part o[illegible]

	Rörsch and Fassbender.	Schwanert.	Liebermann.	[illegible]
Substance examined	Liver of decomposing cadaver and of fresh liver of ox.	Decomposing liver, kidney, and stomach.	Putrefying stomach and contents.	Muscle macerated in water.
Solvent	Ether (acid and alkaline).	Ether (alkaline).	Ether (acid and alkaline).	Ether (alkal[illegible]
Residue	Amorphous, not bitter.	Liquid, volatile; repulsive taste.	Resinous, brownish, soluble in water, acid taste.	Greasy brown mass, with [illegible]
Tannic acid.	White precipitate.	Gradual cloudiness.	White precipitate.	White precip[illegible]
Gold chloride	———	Bluish-yellow precipitate.	———	Yellow cryst[illegible] precipit[illegible]
Platinum chloride	Yellowish precipitate.	Dirty yellow [illegible] mass.	———	Brownish precipit[illegible]
Iodine in potassium iodide.	Yellowish brown precipitate.	Clear brown precipitate.	Yellow to dark brown.	Kermes [illegible] precipit[illegible]
Fröhde's reagent	———	Splendid blue, later green.	———	———
Phosphomolybdic acid.	Yellow precipitate, on warming green; with NH_4OH, blue.	Yellow precipitate, with NH_4OH, blue.	Yellow precipitate.	Heavy floc[illegible] precipit[illegible]
Sulphuric acid	———	Dirty brownish-yellow, unchanged on warming.	Colorless, then slight reddish violet color.	———
Sulphuric acid and potassium bichromate.	———	Reddish-brown, then grass green.	———	———
Nitric acid	———	Yellow.	Yellow spots on evaporation.	———
Hydrochloric acid	———	Deliquescent white needles.	———	———
Mercuric chloride	———	White crystalline precipitate.	White cloudiness.	Curdy white [illegible]
Potassium mercuric iodide.	———	Dirty white precipitate.	———	———
Chlorine water	———	———	Heavy white precipitate.	———
Picric acid	———	———	———	———
Physiological action.	———	———	When fed to pigeons no effect.	Caused myd[illegible] increase in [illegible] of heart [illegible]

Table II.—Ptomaines in Toxicological Examinations.

Note.—The greater part of this table has been taken direct from Gräbner's Inaugural Dissertation.

	Kersch and Fassbender.	Schwanert.	Liebermann.	Zoelter and Sonnenschein.	v. Gelder.	Brouardel and Boutmy.				Baumert (Liebermann).	Otto.
Substance examined	Liver of decomposing cadaver and of fresh liver of ox.	Decomposing liver, kidney, and stomach.	Putrefying stomach and contents.	Muscle macerated in water.	Liver, kidney, stomach and intestine of an exhumed arsenic-containing body.	Cadaver. Death by asphyxia	Cadaver. Death by hydrocyanic acid.	Cadaver. In water 18 months.	Parts of putrefying goose and cadaver.	.....	.....
Solvent	Ether (acid and alkaline).	Ether (alkaline).	Ether (acid and alkaline).	Ether (alkaline).	.....	.....	.....	.....	.....	Ether (acid .	Petroleum ether (alkaline).
Residue	Amorphous, not bitter.	Liquid, volatile; repulsive taste.	Resinous, brownish, soluble in water, acid taste.	Greasy brownish mass, with crystals.	Brown extract.	.....	.....	Alkaline.	Alkaline, volatile liquid; odor that of urine of mice.	Yellow, amorphous; taste sharp, bitter.	Bright yellow oil.
Tannic Acid.	White precipitate.	Gradual cloudiness.	White precipitate.	White precipitate.	White precipitate.	White precipitate.		.....	White precipitate.	Same as colchicine; soluble in alcohol.	.....
Gold Chloride	.....	Bluish-yellow precipitate.	.....	Yellow crystalline precipitate.	Brown precipitate.	Yellow precipitate.		.....	Violet precipitate.	Same as colchicine.	A precipitate.
Platinum Chloride	Yellowish precipitate.	Dirty yellow six-sided stars.	.....	Brownish-yellow precipitate.	Id.	o		.....	.....	A precipitate, colchicine = 0.	Id.
Iodine in Potassium Iodide.	Yellowish-brown precipitate.	Clear brown precipitate	Yellow to dark brown.	Kermes-brown precipitate.	Id.	Kermes-brown precipitate.		.....	Kermes-brown precipitate.	Same as colchicine.	.....
Fröhde's Reagent	.....	Splendid blue, later green.	.....	.....	.....	o		.....	Orange-red.	.....	.....
Phosphomolybdic Acid.	Yellow precipitate, on warming green; with NH_4OH, blue.	Yellow precipitate, with NH_4OH, blue.	Yellow precipitate.	Heavy flocculent precipitate.	Yellow precipitate.	White precipitate.		.....	.....	Same as colchicine, blue with NH_4OH.	.....
Sulphuric Acid	.....	Dirty brownish-yellow, unchanged on warming.	Colorless, then slight reddish violet color.	.....	On warming becomes yellow.	On warming violet.	In the cold brownish violet.	Colorless; on warming, violet.	.....	Yellow color.	.....
Sulphuric Acid and Potassium Bichromate.	.....	Reddish-brown, then grass green.	....	.....	.....	Intense green.		....	No odor of butyric acid.	....	.....
Nitric Acid	.....	Yellow.	Yellow spots on evaporation.	.....	Id.	Golden-yellow.		.....	.....	Dark yellow color, concentrated HNO_3= carmine-red which with water gives yellow.	.....
Hydrochloric Acid	.....	Deliquescent white needles.	.....	.....	.....	.....		Cherry-red on heating.	Colorless.	.....	A precipitate.
Mercuric Chloride	.....	White crystalline precipitate.	White cloudiness.	Curdy white precipitate.	White precipitate.	o		.....	.....	.....	.....
Potassium Mercuric Chloride	.....	Dirty white precipitate.	.....	.....	Id.	Yellow precipitate.		Abundant precipitate.	.....	Same as colchicine.	.....
Chlorine Water	.....	.....	Heavy white precipitate.	.....	Id.	.....		.....	.....	A precipitate, colchicine = 0.	.....
Picric Acid	.....	.....	.....	.....	.....	Abundant yellow precipitate. Iodic acid is reduced. Silver Nitrate, white precipitate with reduction of silver. Ferric Chloride = 0.	o	Potassium Ferrocyanide is reduced. $H_2SO_4 + BaH_2O_2$ = brick-red; on warming, violet.	....	Zeisel's reaction=0, colchicine, green. Ferric salts = blue. Millon's reagent showed presence of peptone.	.....
Physiological Action.	.....	.....	When fed to pigeons no effect.	Causes mydriasis and increase in the rate of heart beat.	.....	.....	In frogs produces slowing of heart, paralysis, death.	Non-poisonous.	Non-poisonous.	Non-poisonous.	Intensely poisonous.

Table III.—Reactions of Selmi's Ptomaines.

Solvent.	Ether (acid). a.	Ether (alkaline). b.	Chloroform (alkaline). c.	Amyl Alcohol (alkaline). d.
Tannic Acid .	Precipitate.	.....	.....	.....
Iodine in Hydriodic Acid	Id.	Precipitates in two crystalline forms.	Crystalline precipitate	Reddish-brown precipitate with deliquescing crystals.
Gold Chloride .	Id.	A precipitate.	.....	Yellowish precipitate.
Mercuric Chloride . .	Id.	White precipitate.	.....	Whitish precipitate.
Phosphomolybdic Acid .	.....	Violet or dark blue.	.....	.....
Concentrated Sulphuric Acid (warmed).	Violet red.	Violet or yellowish-brown.	Reddish coloration.	.....
Sulphuric Acid and Potassium Dichromate.	.....	Gradually passes into green.	.....	.....
Iodic Acid . . .	Reduction.	Reduction.	Reduction.	Reduction.
Iodic Acid + Sulphuric Acid + Soda.	Rose colored salt.	Violet.	.....	.....
Nitric Acid . . .	Yellow (on warming stronger).	.....	.....	Slight yellow.
Hydrochloric Acid + Sulphuric Acid.	Slight violet.	Violet color with odor of hawthorn.	.....	.....
Sulphuric Acid + Bromine	.....	Red (permanent)	As with sulphuric acid.	.....
Fröhde's Reagent . .	.....	Yellowish-brown to violet or yellow.	Red	.....
Ferric Chloride . .	.....	Cloudiness.	.....	Rose colored precipitate.
Hydrochloric Acid . .	.....	Slight violet, more distinct on standing.	.....	.....
Phosphoric Acid (diluted)	.....	On warming violet color.	.....	.....
Sulphuric Acid (diluted)	Violet passing into yellow; odor of hawthorn.	Violet, if stirred becomes black.	.....	.....
Potassium Platinic Cyanide.	}	} Occasionally precipitates.	}	.....
Potassium Argentic Cyanide.				
Platinum Chloride. .				
Potassium Dichromate .				

produces violent convulsions. He estimates that the amount of poisonous alkaloids formed in the intestines of a healthy man each twenty-four hours would be quite sufficient to kill if it was all absorbed. He proposes the term stercoræmia for that condition which results from arrest of excretion from the intestine.

It is not supposed by any one at present that all the symptoms of so-called uræmic poisoning result from retention of urea alone, but the urine contains substances a thousand-fold more poisonous than urea, and these also are retained. We take the amount of urea retained as an evidence of the extent of danger, because we can estimate the amount of urea definitely just as we take the amount of carbonic acid gas in the air in making an estimate of the extent to which it is vitiated, and not because we believe that either the urea in the one case, or the carbonic acid in the other, is really the dangerous substance.

That the development of infectious diseases is largely dependent upon the condition of the person into whom the germs are introduced is well known. Two men may drink of the same water infected with the bacillus of typhoid fever, and yet one will have the disease, and the other will escape. The importance of the personal equation in acquiring infectious diseases is fully recognized. That the difference in susceptibility may be due to the relation between the formation and excretion of these poisons generated within the body, we think highly probable.

CHAPTER IX.

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